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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07H 15/00 — A2

(11) International Publication Number: WO 99/29706

(43) International Publication Date: 17 June 1999 (17.06.99)

(21) International Application Number: PCT/US98/25788

(22) International Filing Date: 4 December 1998 (04.12.98)

(30) Priority Data:
60/067,877 8 December 1997 (08.12.97) US

(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application
US 60/067,877 (CON)
Filed on 8 December 1997 (08.12.97)

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: DISALICYLATE ANALOG BASED SIALYL LEWIS^x MIMETICS

(57) Abstract

The present invention discloses medicaments that are selectin–ligand structural mimetics that bind to certain selectins wherein the mimetics may lack the sialic acid and/or fucose of the natural selecting ligand, sialyl Lewis^x (sLe^x), but have a structure capable of mimicking the structural features necessary for selectin recognition. In particular, the invention compounds mimic the key structural features of the oligosaccharides responsible for selectin–mediated cell adhesion. These features consist of the charge–distance–coordination relationship between the carboxylic acid functionality of sialic acid at a distance of 8–12 angstroms of the L–fucose moiety. The invention compounds are disalicylate, its analogs, and disalicylate–based C–glycoside compounds. The present invention also discloses methods of treating selectin–mediated disorders comprising administering the compounds disclosed.

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Disalicylate Analog Based Sialyl Lewis^x Mimetics

FIELD OF THE INVENTION

This invention relates generally to the field of medicinal chemistry, and specifically to medicaments that are characterized by their capacity to bind to one or more of the three known selectins: E, L, and P-selectin. The medicaments consist of disalicylates, and their analogs, including carbon-glycoside containing analogs. Such medicaments have significant applications for diagnosis prophylactic and therapeutic treatment of certain selectin-mediated diseases including cancer, auto-immunity, and inflammation.

BACKGROUND OF THE INVENTION

A large body of data has been accumulated that establishes a family of receptors, the selectins (LEC-CAMs) in certain diseases including cancer, auto-immunity, and in the inflammatory response. There are presently three known members of this family, L-Selectin (LECAM-1, LAM-1, gp90MEL), E-Selectin (LECAM-2, ELAM-1) and P-Selectin (LECAM-3, GMP-140, PADGEM). The physical, molecular, biochemical, and physiological characteristics of this family of receptors is well known in the art. In particular, PCT application Publ. No. WO97/30984 and references therein describe the sequence of the known members of

the selectin family of receptors and its homology to other known proteins, the role of selectins in inflammation, site-specific lymphocyte extravasation, lung injury, and thrombosis. It is also disclosed in those references that E-selectin is transiently expressed on endothelial cells in response to IL-1 and Tumor Necrosis Factor (TNF), suggesting a role for this receptor in the initial neutrophil-extravasation response to infection and injury. Furthermore, blocking the E-selectin receptor with specific antibodies prevents the influx of neutrophils in a primate model of asthma preventing airway obstruction resulting from the inflammatory response. PCT application Publ. No. WO97/30984 and references therein are incorporated herein by reference.

Several different groups have published papers regarding E-selectin ligands. Lowe *et al.*, (1990) demonstrated a positive correlation between E-selectin dependent adhesion of HL-60 cell variants and transfected cell lines, with their expression of the sialyl Lewis x (sLe^x) oligosaccharide, NeuNAc -2-3-Gal- 1-4(Fuc -1-3)-GlcNAc. By transfecting cells with plasmids containing an -(1,3/1,4) fucosyltransferase, they were able to convert non-myeloid COS or CHO lines into sLe^x-positive cells that bind in an E-selectin dependent manner. Walz *et al.*, (1990) were able to inhibit the binding of an E-selectin-IgG chimera to HL-60 cells with a monoclonal antibody directed

against sLe^x or by glycoproteins with the sLe^x structure, but could not demonstrate inhibition with CD65 or CD15 antibodies. Both groups concluded that the sLe^x structure is the ligand for E-selectin.

Information regarding the DNA sequences encoding endothelial cell-leukocyte adhesion molecules are disclosed in PCT published application W090/13300 published November 15, 1990 incorporated herein by reference. The PCT publication cites numerous articles that may be related to endothelial cell-leukocyte adhesion molecules. The PCT publication discloses methods of identifying E-selectin ligands, as well as methods of inhibiting adhesion between leukocytes and endothelial cells using such ligands. Recent publications regarding selectin ligands describe the use of L-selectin as an indicator of neutrophil activation (Butcher *et al.*, U.S. Patent 5,316,913 issued May 31, 1994), and assays for inhibition of leukocyte adhesion (Rosen *et al.*, U.S. Patent 5,318,890 issued June 7, 1994). These publications are hereby incorporated by reference.

The ligand for E-selectin, sLe^x, is thought to consist of at least sialic acid, fucose, and N-acetyl lactosamine. Lactosamine consists of galactose and 2-amino-2-deoxyglucose. Sialic acid and fucose are bound to the galactose and glucosamine moieties of lactosamine, respectively. Ligands that

bind to the other selectins share similar structural features. Considering the obvious medical importance of selectin ligands, significant effort has been, and continues to be, expended to identify the critical physical/chemical parameters associated with selectin ligands that enhance, or that are required for their activity (DeFrees, S.A., *et al.*, J. Am. Chem. Soc., (1993) 115:7549). In no small part this effort is being driven by the need to have selectin ligands that are inexpensive to produce (see U.S. Patent 5,296,594 issued March 22, 1994; Allanson, N.M. *et al.*, Tetrahedron Lett., (1993) 34:3945; Musser, J.H. et al., Current Pharmaceutical Design (1995) 221-232). It is generally thought that it will be prohibitively expensive to commercially produce naturally occurring sLe^x by either enzymatic or chemical synthesis because of the number of sophisticated reactions involved.

The selectin family of adhesion molecules participates in acute inflammation by initiating neutrophil rolling on activated endothelial cells. This is particularly evident in studies of ischemia reperfusion injury, where P-selectin appears to be important in neutrophil recruitment to damaged tissue. The presence of L-selectin and E- or P-selectin ligands on mononuclear cells has implicated these receptor-ligand interactions in chronic inflammation. This has been supported by the finding of chronic expression of E-selectin in

dermatological conditions, and P-selectin expression on joint synovial endothelium derived from rheumatoid arthritis patients. L. Lasky Annu. Rev. Biochem. 64:113-39 (1995); "Selectin Family of Adhesion Molecules" by Michael Forrest and James C. Paulson in Physiology and Pathophysiology of Leukocyte Adhesion, Ed. by D. Niel Grangier and Deert Schmid-Schönbein, Oxford University Press, N.Y., N.Y. (1995).

SUMMARY OF THE INVENTION

A first object of the invention is the description of medicaments that are selectin ligand structural mimetics that bind to certain selectins wherein the mimetics may lack the sialic acid and/or fucose of the natural selectin ligand, sialyl Lewis^x (sLe^x), but have a structure capable of mimicking the structural features necessary for selectin recognition. In particular, the invention compounds mimic the key structural features of the oligosaccharides responsible for selectin-mediated cell adhesion. These features are thought to consist of the charge-distance-coordination relationship between the carboxylic acid functionality of sialic acid at a distance of 8-12 angstroms of the L-fucose moiety. The invention compounds are disalicylate, its analogs, and disalicylate-based C-glycoside compounds.

A second object of the invention is to provide a composition comprising selectin ligand medicaments bound to a detectable label and/or bound to a pharmaceutically active drug such as an anti-inflammatory drug.

A third object of the invention is to provide a pharmaceutical formulation containing selectin ligand medicaments which is useful in treating certain selectin-mediated diseases.

A fourth object of the invention is to provide a description of methods to treat or diagnose disease.

A fifth object of the invention is to provide compositions and methods to determine the site of inflammation by administering labeled formulations of the type referred to above.

Another object of the invention is that the ligands can be labeled and the labeled ligands used in an assay to detect the presence of selectins in a sample.

These and other objects, advantages and features of the present invention will become apparent to those persons skilled in the art upon reading the details of the synthesis, structure, formulation and usage as more fully set forth below.

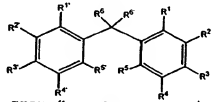
DEFINITIONS

In accordance with the present invention and as used herein, the terms used herein are defined according to their standard scientific meaning. Further definitions consistent with the present specification are provided in Publ. No. WO97/30984.

"-Ar-" refers to a phenyl, optionally substituted.

"-alk-" refers to an alkyl linking group which is selected from lower alkyl, and cycloalkyl. Suitable "-alk-" groups include $-C(CH_3)_2-$, and $-CH_2-\bigcirc-$.

"Disalicylate" or "Disalicylate Analog" refers to structure depicted below:



"Protecting group" refers to a group protecting one or several inherent functional groups. Suitable "protecting groups" will depend on the functionality and particular chemistry used. Examples of suitable protecting groups will be readily apparent to skilled artisans, and are described, for example, in Greene and Wutz, Protecting Groups in Organic Synthesis, 2d ed., John Wiley & Sons, NY (1991), which is incorporated herein by reference. Suitable -O- protecting

groups can be found in the above book. Preferred such protecting groups include acetate and benzyl.

DETAILED DESCRIPTION OF THE INVENTION

Throughout the description of the invention reference is made to certain publications including scientific articles and patents or patent applications. It is the intent that each of these publications be incorporated by reference in their entirety when referred to in the specification.

Before describing the present invention it is to be understood that this invention is not limited to the particular compositions, methods or processes described as such compositions and methods may, of course, vary.

As used in this specification and the appended claims, the singular forms "a", "an" and "the" include the plural unless the context clearly dictates otherwise. Thus, for example, reference to "a tethered compound" includes mixtures of such compounds, reference to "an E-selectin", "a P-selectin", or "an L-selectin" includes reference to respective mixtures of such molecules, reference to "the formulation" or "the method" includes one or more formulations, methods and/or steps of the type described herein and/or which will become apparent to those persons skilled in the art upon reading this disclosure.

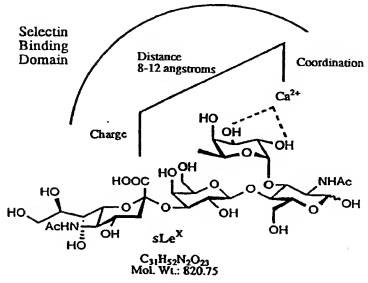
Some standard abbreviations used in connection with the present invention include: BSA, bovine serum albumin; DEAE, diethylaminoethyl; DMSO, dimethylsulfoxide; DMF, N,N-dimethylforamide; DCE, dichloroethane; E-selectin or ELAM-1, endothelial/leukocyte adhesion molecule-1; HPTLC, high performance thin layer chromatography; L-selectin or LECAM-1, leukocyte/endothelial cell adhesion molecule-1; MOPS, 3-[N-Morpholino)-propanesulfonic acid; NANA, N-acetylneuraminic acid; PVC, polyvinylchloride; TLC, thin layer chromatography; TFA, trifluoro-acetic acid; Tris, tris (hydroxy-methyl) aminomethane.

Development of the Invention

It is worth noting that while the invention compounds were selected for their capacity to bind to certain selectins, and that therefore this property contributes to their medical activity, it cannot, however, be excluded that they are also exerting their favorable medical effects, either in parallel or in tandem, through additional mechanisms of action. Thus, the skilled practitioner of this art will appreciate that a key aspect of the subject invention is the description of novel medicaments, and that Applicants intend not to be bound by a particular mechanism of action that may account for their prophylactic or therapeutic effects.

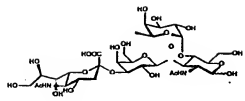
E-selectin has a lectin like domain that recognizes the Sialyl Lewis x (sLe^x) tetrasaccharide epitope as shown below in Structure II.

II



The ability of sLe^x to bind E-selectin is described by Lowe *et al.*, Cell (1990) 63:475; Phillips *et al.*, Science (1990) 250-1130; Walz *et al.*, Science (1990) 250:1132; and Tyrrell *et al.*, Proc. Natl. Acad. Sci. USA (1991) 88:10372.

It has also been shown (Berg *et al.*, J. Biol. Chem. (1991) 265:14869; Handa *et al.*, Biochem. Biophys. Res. Commun. (1991) 181:1223) that both E-selectin and P-selectin recognize the isomeric tetrasaccharide sLe^a shown below as Structure III.



sLe^a
$C_{31}H_{52}N_2O_{23}$
Mol. Wt.: 820.7314

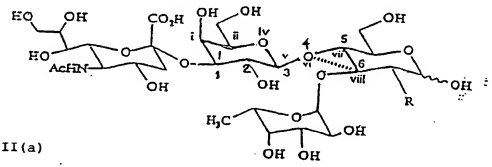
III

L and P-selectin also bind to sLe^x containing ligands, although these selectins have specificity toward a wider variety of natural ligands containing sialylated and sulfated Le^x, and Le^a structures as well as other sulfated or charged carbohydrates. Varki et al. Proc. Nat'l Acad. Sci. USA 91:7390-7397 (1994).

A key step in developing the compounds of the present invention was the realization that both sLe^x and sLe^a share a structural similarity in their three dimensional arrangements.

Specifically, we observed that sialic acid and fucose, two functional epitopes in these tetrasaccharides, are juxtaposed in space in a way suitable for recognition by the selectins. Most importantly, for both tetrasaccharides we identified 4 to 12 atoms associated with the lactose core of the tetrasaccharides that functionally separate sialic acid from fucose. We postulated that compounds such as those described and claimed herein, would produce molecules with selectin binding activity.

For instance, a close structural examination of sLe^x (shown in II) or a modification thereof wherein R = OH (sLe^xGlc) indicates that the epitopes i.e., α-Neu5Ac and L-Fucose, are linked through six atoms (Nos. 1-6) or eight atoms (Nos. i-viii) as shown in Structure II (a) below



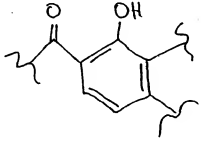
II(a)

wherein R is -NHAc or -OH.

Based on this discovery, we deduced that the corresponding epitopes on the lectin domain of the selectins, are spaced in a

similar three-dimensional configuration such that sLe^x and sLe^a present the fucose and sialic acid functionalities in a special relationship placing them on a single face with a spacing of 10-12 angstroms measured between the carbonyl carbon of the carboxylic acid on sialic acid and the C-3 of fucose. Rao et al. (1994),.J. Bio. Chem. 269(31):19663

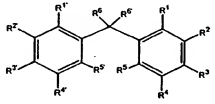
Applicants believe that the carboxylic acid portion of sialic acid is important for binding. Thus, mimics of sialic acid include moieties containing carboxylic acids, esters and amides. It also includes a vinylagous acid that can mimic the acid functionality, such as the group shown below:



Other sialic acid mimics, also referred to as "A" in the general description, can be in the form of moieties containing sulfates, sulfonates, phosphates, phosphonates, sulfonamides, nitrates, other carboxylic acid equivalents, and the like. Other acid mimics include B groups, particularly B groups that contain acids and sulfates.

The compounds of the present invention are designed based on the novel concept that selectin inhibitors need not always

possess the same type of complex carbohydrate structural features normally associated with the natural epitopes. The essential feature of the inhibitors disclosed in the present invention is that they not all contain the sialic acid and/or fucose present in the natural epitopes. Rather, the compounds of the invention all contain charged and coordinating groups, and/or a charge cluster distribution, separated by specific distances to allow for binding between those functional groups and receptors on natural selectins. The compounds are represented by the following general structural formula I:



wherein:

R^1, $R^{1'}$, R^2, $R^{2'}$, R^3, $R^{3'}$, R^4, $R^{4'}$, R^5, $R^{5'}$, R^6, and $R^{6'}$ are independently selected from the group consisting of:

A, B, Y-B, Y-C, -H, -OH, lower alkoxy, lower aryloxy, lower aralkoxy, lower alkoxyaryl, amino, alkyl of 1 to 4 carbon atoms optionally substituted with 1 to 2 lower alkyl groups,

$-W((CH_2)_n-A)_t$, $-W((CH_2)_m-(CHR^9)_q-(CH_2)_n-A)_t$,

$-O-CH_2-C\equiv C-A$, $-N(Ac)-CH_2-C\equiv C-A$, $-NH-CH_2-C\equiv C-A$,

$-N(CH_2-C\equiv C-A)_2$, $-N(Ac)CH_2Ar-A$, $-NHCH_2Ar-A$, $-N(CH_2Ar-A)_2$, $-OCH_2Ar-A$, $-(C=O)(CH_2)_m-A$;

R^2 and R^3 or $R^{2'}$ and $R^{3'}$ may be taken together with the carbon atoms to which they are covalently bound to form a five or six membered ring optionally containing a heteroatom selected from the group consisting of -O-, -S-, and $-NR^{16}-$ wherein said five or six membered ring may further be substituted with one or more substituents selected from the group consisting of R^{16};

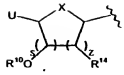
R^5 and $R^{5'}$ may optionally be taken together as $-CH_2-$, $-(C=O)-$, $-(CR^{16}_2)-$, -O-, -S-, and $-NR^{16}-$;

R^6 and $R^{6'}$ may optionally be taken together with the carbon atom to which they are covalently bound to form a $-(C=O)-$, $-(C=CH_2)-$, $-(C=C(R^{16})_2)-$, or $-(C=NR^{16})-$ group;

wherein:

A is selected from the group consisting of $-(C=O)R^{11}$, sialic acid, Kemp's acid, quinic acid, -B, $-SO_3M$, $-OSO_3M$, $-SO_2NH_2$, $-PO_3M_2$, $-OPO_3M_2$, $-NO_2$, saturated or unsaturated carboxylic acids of 1 to 4 carbon atoms, optionally substituted with 1 to 2 hydroxyl groups, and esters and amides of the carboxylic acid substituent;

B is



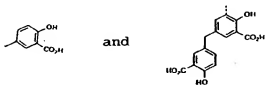
wherein:

U is selected from the group consisting of $-R^9$, $-R^{10}$, $-CH_2OR^{10}$, $-CH_2O$-protecting group, $-COOR^{11}$, $-CON(R^{11})_2$, and $-COOM$;

Y-B is selected from the group consisting of

- $W((CH_2)_n\ (C=O)CH_2-B)_t$, - $W((CH_2)_n\ (C=C(R^{15})_2)-CH_2-B)_t$,
- $W((CH_2)_n\ \underset{\displaystyle CH(R^{11})_2}{\underset{|}{CH}}-CH_2-B)_t$, - $W((CH_2)_n\ \underset{\displaystyle C(R^{11})_2OR^{11}}{\underset{|}{CR^{11}}}-CH_2-B)_t$,
- $W((CH_2)_n\ \underset{\displaystyle C(R^{11})_2OR^{11}}{\underset{|}{\overset{\displaystyle OR^{11}}{\overset{|}{C}}}}-CH_2-B)_t$, - $W((CH_2)_n\ C(R^{11})_2-CH_2-B)_t$,
- $W((CH_2)_n\ \underset{\displaystyle R^{11}}{\underset{|}{\overset{\displaystyle COOR^{11}}{\overset{|}{C}}}}-CH_2-B)_t$, - $W((CH_2)_n\ \underset{\displaystyle R^{12}}{\underset{|}{\overset{\displaystyle C(R^{11})_2R^{12}}{\overset{|}{C}}}}-CH_2-B)_t$,
- $W((CH_2)_n\ CR^{11}(OR^{11})CH_2-B)_t$,
- $CO(CH_2)_nCO-B$, and
- $NHCO(CH_2)_nCONH-B$;

Y-C is selected from the group consisting of



and ;

W is selected from the group consisting of a covalent bond, $-CH_2-$, -(C=O)-, -(C=O)NH-, -O-, -N< -S-, -NH-, and -NAc-;

R^9 is lower alkyl of 1 to 4 carbon atoms;

each n is independently selected from the group 0, 1, 2, and 3;

each m is independently selected from the group 0, 1, 2, 3, and 4;

each q is independently selected from the group 0, 1, and 2;

each s is independently selected from the group 1, 2, and 3;

each z is independently selected from the group 1 and 2;

each t is independently selected from the group 1 and 2, with the proviso that when W is -N< , then t is 2, and for all other definitions of W, t is 1;

R^{10} is selected from the group consisting of -H, $-R^{11}$, $-SO_3M$, $-(C=O)R^{11}$, $-SO_2NH_2$, $-PO_3M_2$, -alk-$COOR^{13}$, alk-$CON(R^{11})_2$, and -O-carbohydrate;

R^{11} is independently selected from the group consisting of -H, lower alkyl of 1 to 4 carbon atoms, cyclic alkyl of 5 to 6 carbon atoms, heterocyclic alkyl of 4 to 5 carbon atoms and 1 to 2 heteroatoms, aryl and aralkyl;

R^{12} is selected from the group consisting of $-N(R^{11})_2$ and $-SR^{11}$;

R^{13} is selected from the group consisting of R^{11} and M;

R^{14} is selected from the group consisting of -H and $-OR^{10}$, with the proviso that when z is 2, then together the two R^{14} groups may form a double bond;

R^{15} is independently selected from the group consisting of $-R^{11}$ and -COOH;

R^{16} is independently selected from the group consisting of $-R^9$, $-R^{10}$, $-CH_2OR^{10}$, $-CH_2O$-protecting group, $-COOR^{11}$, $-CON(R^{11})_2$, and -COOM;

M is selected from the group consisting of Na^+, K^+, Mg^{2+}, and Ca^{2+};

M' is selected from the group consisting of -H, -M, and R^9;

X is selected from the group consisting of -O-, -S-, $-C(R^{11})_2-$, and $-N(R^{11})-$; and pharmaceutically acceptable salts thereof with the provisos that:

(a) at least one of R^1, R^2, R^3, $-R^4$, R^5, $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{5'}$, R^6, and $R^{6'}$ is selected from the group consisting of saturated or

unsaturated carboxylic acids of 1 to 4 carbon atoms, optionally substituted with 1 to 2 hydroxyl groups, and esters and amides of the carboxylic acid substituent; and

(b) at least one of R^1, R^2, R^3, R^4, R^5, $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{5'}$, R^6, and $R^{6'}$ is a substituent containing a B group.

The structures that contain the appropriate reactive functions can be reacted with suitably protected hydrophobic carriers like ceramide or a ceramide mimic, steroids, diglycerides or phospholipids to form other medically useful molecules.

The compounds can act as antagonist ligand molecules, i.e. biochemical blocking agents, by binding to selectins and preventing circulating leukocytes from binding to endothelial cells, thereby preventing a primary event involved in certain diseases, including cancer, and particularly metastatic cancers, conditions associated with inflammation, such as reperfusion injury, septic shock, hypovolemic or traumatic shock, ARDS, rheumatoid arthritis, asthma, inflammatory bowel disease, dermatitis, pulmonary inflammation, lung vasculitis, auto-immune conditions such as diabetes, and tissue rejection and other conditions such as obesity, cardiac injury, and thrombosis. Agonist ligands have the opposite effect.

The compounds of structural formula I can be bound to known drugs, for example anti-inflammatory drugs so as to target the drug-selectin ligand complex to a particular site of disease. Additionally, they can be formulated to provide compositions useful in assaying a sample for the presence of selectins such as E, L and/or P-selectin, or to detect the site of inflammation in a patient, or to treat acute inflammation (or treating the inflammatory symptoms of certain diseases) or other diseases involving the interaction of selectins on appropriate cell types.

Preferred are compounds where R^1, $R^{1'}$, R^2, $R^{2'}$, R^5, $R^{5'}$, R^6, and $R^{6'}$ are -H; $R^{3'}$ is -OH, R^4 and $R^{4'}$ are $-COOR^{11}$, R^3 is $-W((CH_2)_m-(CHR^9)_q-(CH_2)_m-A)_t$ or $-W((CH_2)_n-B)_t$, and -W is -O-. Most preferred are said compounds where m is 1, q is 1, R^9 is $-CH_3$, A is selected from the group consisting of B, and t is 1.

Also preferred are compounds where R^1, $R^{1'}$, $R^{2'}$, R^5, $R^{5'}$, R^6, and $R^{6'}$ are -H, R^3 and $R^{3'}$ are -OH, R^4 and $R^{4'}$ are $-COOR^{11}$, R^2 is $-W((CH_2)_m-(CHR^9)_q-(CH_2)_m-A)_t$ or $-W((CH_2)_n-B)_t$, and -W a covalent bond. Most preferred are said compounds where m is 1, q is 1, R^9 is $-CH_3$, A is selected from the group consisting of B, and t is 1.

Also preferred are compounds where R^1, $R^{1'}$, R^2, $R^{2'}$, R^5, $R^{5'}$, R^6, and $R^{6'}$ are -H, R^3 and $R^{3'}$ are $-W((CH_2)_m-(CHR^9)_q-(CH_2)_m-A)_t$ or $-W((CH_2)_n-B)_t$, R^4 and $R^{4'}$ are $-COOR^{11}$, and -W is -O-. Most

preferred are said compounds where m is 1, q is 1, R^9 is $-CH_3$, A is selected from the group consisting of B, and t is 1.

Also preferred are compounds where R^1, $R^{1'}$, R^5, $R^{5'}$, R^6, and $R^{6'}$ are -H, R^2 and $R^{2'}$ are independently selected from $-W((CH_2)_m-(CHR^9)_q-(CH_2)_m-A)_t$ or $-W((CH_2)_n-B)_t$, R^3 and $R^{3'}$ are -OH, R^4 and $R^{4'}$ are $-COOR^{11}$, and -W a covalent bond. Most preferred are said compounds where m is 1, q is 1, R^9 is $-CH_3$, A is selected from the group consisting of B, and t is 1.

Also preferred are compounds where R^1, $R^{1'}$, R^2, $R^{2'}$, R^5, $R^{5'}$, R^6, and $R^{6'}$ are -H; R^3 is $-W((CH_2)_m-(CHR^9)_q-(CH_2)_m-A)_t$ or $-W((CH_2)_n-B)_t$, $R^{3'}$ is $-W((CH_2)_m-(CHR^9)_q-(CH_2)_m-A)_t$ or $-W((CH_2)_n-B)_t$, R^4 and $R^{4'}$ are $-COOR^{11}$, and -W is -O-. Most preferred are said compounds where m is 1, q is 1, R^9 is $-CH_3$, the R^3 -A and the $R^{3'}$ -A are independently selected from the group consisting of B, and t is 1.

Also preferred are compounds where R^1, $R^{1'}$, $R^{2'}$, R^5, $R^{5'}$, R^6, and $R^{6'}$ are -H, R^2 is $-W((CH_2)_m-(CHR^9)_q-(CH_2)_m-A)_t$ or $-W((CH_2)_n-B)_t$, $R^{3'}$ is $-W((CH_2)_m-(CHR^9)_q-(CH_2)_m-A)_t$ or $-W((CH_2)_n-B)_t$, R^3 is -OH; R^4 and $R^{4'}$ are $-COOR^{11}$, the R^2 -W is a covalent bond, the $R^{3'}$ W is -O-. Most preferred are such compounds where m is 1, q is 1, R^9 is $-CH_3$, t is 1, and the R^2 -A and the $R^{3'}$ -A are independently selected from the group consisting of B.

Also preferred are compounds where R^1, $R^{1'}$, R^5, $R^{5'}$, R^6, and $R^{6'}$ are -H, R^2 is $-W((CH_2)_m-(CHR^9)_q-(CH_2)_m-A)_t$ or $-W((CH_2)_n-B)_t$, $R^{2'}$

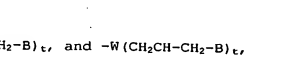
is $-W((CH_2)_m-(CHR^9)_q-(CH_2)_m-A)_t$ or $-W((CH_2)_n-B)_t$, R^3 and $R^{3'}$ are -OH, and R^4 and $R^{4'}$ are $-COOR^{11}$. Most preferred are said compounds where -W is a covalent bond, m is 1, q is 1, R^9 is $-CH_3$, the R^2 -A and the $R^{2'}$ -A are independently selected from the group consisting of B, and t is 1.

Preferred R^{11} are -H or $-CH_2-CH_3$. A preferred M is Na^+. Preferred M' are -H, Na^+, and $-CH_3$.

Also preferred are compounds where R^4 and $R^{4'}$ are saturated or unsaturated carboxylic acids of 1 to 4 carbon atoms, optionally substituted with 1 to 2 hydroxy groups, and esters and amides thereof, and at least one of R^2, $R^{2'}$, R^3, $R^{3'}$, R^6, and $R^{6'}$ is selected from the group consisting of

$-W((CH_2)_n-B)_t$,

$-W(CH_2(C=O)CH_2-B)_t$, $-W(CH_2(C=C(R^{15})_2)-CH_2-B)_t$,



where W is a covalent bond or -O-. Most preferred and t is 1, and wherein the B group s is 1 or 2, R^{14} is -H or -OH, X is -O-,

U is $-CH_2OR^{10}$ or $-R^9$, and R^{10} is -alk-COOH, $-SO_3M$, -H, or -alk-COOM.

Preferred R^1, $R^{1'}$, R^2, $R^{2'}$, R^3, $R^{3'}$, R^4, $R^{4'}$, R^5, $R^{5'}$, R^6, and $R^{6'}$ groups include

$-W(CH_2(C=O)CH_2-B)_t$, $-W(CH_2(C=C(R^{15})_2)-CH_2-B)_t$,

$-W(CH_2CH-CH_2-B)_t$, $-W((CH_2)_n-B)_t$

$CH(R^{11})_2$

OR^{11}

$-W(CH_2-C-CH_2-B)_t$, $-W(CH_2C(R^{11})_2-CH_2-B)_t$,

$C(R^{11})_2OR^{11}$

$-W(CH_2-CR_{11}(OR^{11})CH_2-B)_t$, -OH, lower alkoxy, lower aryloxy, lower araloxy, lower alkoxyaryl, and -H. Most preferred are compounds where W is a covalent bond or -O-, and t is 1.

Preferred B groups include those where s is 1 or 2, R^{14} is -H or -OH, X is -O-, U is $-CH_2OR^{10}$ or $-R^9$, and R^{10} is -alk-COOH, $-SO_3M$, -H, or -alk-COOM. Most preferred are those compounds where s is 2. Particularly preferred B groups include glucose, fucose, galactose, mannose, and arabinose.

Preferred s numbers are 1 and 2. Most preferred is 2.

Preferred q numbers are 0 and 1.

Preferred m numbers are 0 and 1.

Preferred n numbers are 0 and 3.

Preferred z numbers are 1.

Preferred R^{10} groups are -H, SO_3M, -alk-$COOR^{13}$, and -O-carbohydrate. Most preferred are -H, $-SO_3M$, and -alk-$COOR^{13}$.

Preferred R^{11} groups are -H, lower alkyl, and lower aralkyl. Most preferred is -H.

A preferred R^{12} group is $-N(R^{11})_2$.

Preferred R^{14} groups are -H and -OH.

Preferred R^{15} groups are -COOH, -H, and $-CH_3$.

A preferred M cation is Na^+.

Preferred M' groups are -H, Na^+, and $-CH_3$.

A preferred X group is -O-.

Preferred U groups are $-CH_2OR^{10}$ and $-R^9$.

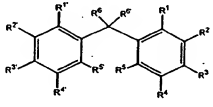
Preferred W groups are a covalent bond and -O-, and t is 1.

Preferred $-W(CH_2(C=C(R^{15})_2)-CH_2-B)_t$ groups are those where W is a covalent bond or -O-, t is 1, and R^{15} is independently -H, $-CH_3$, and -COOH.

Also preferred are compounds where at least one of R^1, $R^{1'}$, R^2, $R^{2'}$, R^3, $R^{3'}$, R^4, $R^{4'}$, R^5, $R^{5'}$, R^6, and $R^{6'}$ is a hydroxy group, and an adjacent group is selected from the group consisting of A.

Preferred compounds also include those prepared in the Examples and those found in Tables A-H.

Another aspect of the present invention comprises a method of treating selectin-mediated disorders comprising the step of administering to a patient in need thereof a therapeutically effective amount of a compound of formula I:



wherein:

R^1, $R^{1'}$, R^2, $R^{2'}$, R^3, $R^{3'}$, R^4, $R^{4'}$, R^5, $R^{5'}$, R^6, and $R^{6'}$ are independently selected from the group consisting of:

A, B, Y-B, Y-C, -H, -OH, lower alkoxy, lower aryloxy, lower aralkoxy, lower alkoxyaryl, amino, alkyl of 1 to 4 carbon atoms optionally substituted with 1 to 2 lower alkyl groups,

$-W((CH_2)_n-A)_t$, $-W((CH_2)_m-(CHR^9)_q-(CH_2)_n-A)_t$,

$-O-CH_2-C\equiv C-A$, $-N(Ac)-CH_2-C\equiv C-A$, $-NH-CH_2-C\equiv C-A$,

$-N(CH_2-C\equiv C-A)_2$, $-N(Ac)CH_2Ar-A$, $-NHCH_2Ar-A$, $-N(CH_2Ar-A)_2$, $-OCH_2Ar-A$, $-(C=O)(CH_2)_m-A$;

R^2 and R^3 or $R^{2'}$ and $R^{3'}$ may be taken together with the carbon atoms to which they are covalently bound to form a five or six membered ring optionally containing a heteroatom selected from the group consisting of -O-, -S-, and $-NR^{16}-$ wherein said five or six membered ring may further be substituted with one or more substituents selected from the group consisting of R^{16};

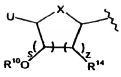
R^5 and $R^{5'}$ may optionally be taken together as $-CH_2-$, $-(C=O)-$, $-(CR^{16}_2)-$, -O-, -S-, and $-NR^{16}-$;

R^6 and $R^{6'}$ may optionally be taken together with the carbon atom to which they are covalently bound to form a $-(C=O)-$, $-(C=CH_2)-$, $-(C=C(R^{16})_2)-$, or $-(C=NR^{16})-$ group;

wherein:

A is selected from the group consisting of $-(C=O)R^{11}$, sialic acid, Kemp's acid, quinic acid, -B, $-SO_3M$, $-OSO_3M$, $-SO_2NH_2$, $-PO_3M_2$, $-OPO_3M_2$, $-NO_2$, saturated or unsaturated carboxylic acids of 1 to 4 carbon atoms, optionally substituted with 1 to 2 hydroxyl groups, and esters and amides of the carboxylic acid substituent;

B is



wherein:

U is selected from the group consisting of $-R^9$, $-R^{10}$, $-CH_2OR^{10}$, $-CH_2O$-protecting group, $-COOR^{11}$, $-CON(R^{11})_2$, and $-COOM$;

Y-B is selected from the group consisting of

$-W((CH_2)_n(C=O)CH_2-B)_t$, $-W((CH_2)_n(C=C(R^{15})_2)-CH_2-B)_t$,

$-W((CH_2)_n CH(CH(R^{11})_2)(OR^{11})-CH_2-B)_t$, $-W((CH_2)_n CR^{11}(C(R^{11})_2OR^{11})-CH_2-B)_t$,

$-W((CH_2)_n C(C(R^{11})_2OR^{11})(COOR^{11})-CH_2-B)_t$, $-W((CH_2)_n C(R^{11})_2-CH_2-B)_t$,

$-W((CH_2)_n C(C(R^{11})_2R^{12})(R^{11})-CH_2-B)_t$, $-W((CH_2)_n C(R^{12})-CH_2-B)_t$,

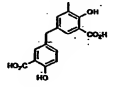
$-W((CH_2)_n CR^{11}(OR^{11})CH_2-B)_t$,

$-CO(CH_2)_nCO-B$, and

$-NHCO(CH_2)_nCONH-B$;

Y-C is selected from the group consisting of

and



W is selected from the group consisting of a covalent bond, $-CH_2-$, $-(C=O)-$, $-(C=O)NH-$, $-O-$, $-N<$, $-S-$, $-NH-$, and $-NAc-$;

R^9 is lower alkyl of 1 to 4 carbon atoms;

each n is independently selected from the group 0, 1, 2, and 3;

each m is independently selected from the group 0, 1, 2, 3, and 4;

each q is independently selected from the group 0, 1, and 2;

each s is independently selected from the group 1, 2, and 3;

each z is independently selected from the group 1 and 2;

each t is independently selected from the group 1 and 2, with the proviso that when W is $-N<$, then t is 2, and for all other definitions of W, t is 1;

R^{10} is selected from the group consisting of -H, $-R^{11}$, $-SO_3M$, $-(C=O)R^{11}$, $-SO_2NH_2$, $-PO_3M_2$, $-alk-COOR^{13}$, $alk-CON(R^{11})_2$, and -O-carbohydrate;

R^{11} is independently selected from the group consisting of -H, lower alkyl of 1 to 4 carbon atoms, cyclic alkyl of 5 to 6 carbon atoms, heterocyclic alkyl of 4 to 5 carbon atoms and 1 to 2 heteroatoms, aryl and aralkyl;

R^{12} is selected from the group consisting of $-N(R^{11})_2$ and $-SR^{11}$;

R^{13} is selected from the group consisting of R^{11} and M;

R^{14} is selected from the group consisting of -H and $-OR^{10}$, with the proviso that when z is 2, then together the two R^{14} groups may form a double bond;

R^{15} is independently selected from the group consisting of $-R^{11}$ and -COOH;

R^{16} is independently selected from the group consisting of $-R^9$, $-R^{10}$, $-CH_2OR^{10}$, $-CH_2O$-protecting group, $-COOR^{11}$, $-CON(R^{11})_2$, and -COOM;

M is selected from the group consisting of Na^+, K^+, Mg^{2+}, and Ca^{2+};

M' is selected from the group consisting of -H, -M, and R^9;

X is selected from the group consisting of -O-, -S-, $-C(R^{11})_2-$, and $-N(R^{11})-$; and pharmaceutically acceptable salts thereof with the proviso that at least three of R^1, R^2, R^3, R^4, R^5, $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{5'}$, R^6, and $R^{6'}$ are not -H.

The compounds of formula I may also be labeled using standard radioactive, fluorescent, enzymatic or other labels for analytical or diagnostic purposes.

Non-steroidal, anti-inflammatory drugs (NSAIDs) such as naproxen or ibuprofen which act as anti-inflammatory agents could be administered bound to the modified ligand and could be administered systemically in smaller amounts than usual while

obtaining an equivalent effect or even greater anti-inflammatory effect at the site of inflammation. Any other drugs which might be attached include, but are not limited to, antibiotics, vasodilators and analgesics. Such a drug delivery system would reduce any systemic effect normally caused by the drug in that the drugs could be administered in amounts of one-half to one-tenth the normal dose and still obtain the same anti-inflammatory result at the site of inflammation.

UTILITY

The invention compounds have considerable utility for the treatment of certain diseases, as set forth herein. However, this is not their only utility. Another utility is identification of particular chemical moieties that are responsible for, or contribute to ligand binding to the different selectins.

It is believed that the compounds of the present invention can be used to treat a wide range of diseases, including diseases such as rheumatoid arthritis and multiple sclerosis. The compositions of the invention should be applicable to treat any disease state wherein the immune system turns against the body causing the white cells to accumulate in the tissues to the extent that they cause tissue damage, swelling, inflammation and/or pain.

The inflammation of rheumatoid arthritis, for example, is created when large numbers of white blood cells quickly enter the joints in the area of disease and attack the surrounding tissues.

Formulations of the present invention might also be administered to prevent the undesirable after effects of tissue damage resulting from heart attacks. When a heart attack occurs and the patient has been revived, such as by the application of anticoagulants or a thrombolytic (e.g., tPA), the endothelial lining where a clot was formed has often suffered damage. When the anti-thrombotic has removed the clot, the damaged tissue beneath the clot and other damaged tissue in the endothelial lining which has been deprived of oxygen become activated. The activated endothelial cells then synthesize the E-selectin receptors within hours of the cells being damaged. The receptors are extended into the blood vessels where they adhere to glycolipid ligand molecules on the surface of white blood cells. Large numbers of white blood cells are quickly captured and brought into the tissue surrounding the area of activated endothelial cells, resulting in inflammation, swelling, and necrosis which thereby decreases the likelihood of survival of the patient.

In addition to treating patients suffering from the trauma resulting from heart attack, patients suffering from actual

physical trauma could be treated with formulations of the invention in order to relieve the amount of inflammation and swelling which normally result after an area of the body is subjected to severe trauma. Other disease states that might be treatable using formulations of the invention include adult respiratory distress syndrome and various types of arthritis and asthma, and dermatitis. After reading the present disclosure, those skilled in the art will recognize other disease states and/or symptoms that might be treated and/or mitigated by the administration of formulations of the present invention.

Radiolabeled compounds of the invention may be prepared in a sterile, non-pyrogenic medium and injected into the bloodstream of a patient at a dose to be determined in the usual way by the physician or radiologist. After a sufficient period for a good balance to have been reached between (i) specificity of binding to activated endothelium compared to non-specific distribution and (ii) total amount of compound on activated endothelium, the compound is imaged in a conventional way, according to the nature of the label used. Use of radiolabeled compounds of the invention could be used to diagnose disease, such as the site of inflammation.

The compounds of the invention could also be used as laboratory probes to test for the presence of a selectin receptor such as a receptor of E, L and/or P-selectin in a

sample. Such probes are preferably labeled such as with a radioactive label. There are a number of known labels including radioactive labeled atoms, e.g. radioactive C, O, N, P, or S, fluorescent dyes and enzyme labels which can be attached to compounds of the invention using known procedures. Labels as well as methods of attaching labels to sugar moieties are disclosed in U.S. Patent No. 4,849,513 issued July 18, 1989 to Smith *et al.* which patent is incorporated herein by reference to disclose labels and methods of attaching labels.

Use and Administration

The compounds of the invention such as various ligands of structural formula I can be administered to a subject in need thereof to treat the subject by either prophylactically preventing inflammation or relieving it after it has begun. The ligands are preferably administered with a pharmaceutically acceptable carrier, the nature of the carrier differing with the mode of administration, for example, oral administration, usually using a solid carrier and I.V. administration in a liquid salt solution carrier. The formulation of choice can be accomplished using a variety of excipients including, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin cellulose, magnesium carbonate, and the like. Oral compositions may be taken in the

form of solutions, suspensions, tablets, pills, capsules, sustained release formulations, or powders. Particularly useful is the administration of the compounds directly in transdermal formulations with permeation enhancers such as DMSO. Other topical formulations can be administered to treat dermal inflammation.

A sufficient amount of compound(s) would be administered to bind to a substantial portion of the selectin expected to cause or actually causing the disease, for example, inflammation so that inflammation can either be prevented or ameliorated. Thus, "treating" as used herein shall mean preventing or ameliorating the appropriate selectin mediated disease.

Typically the compositions of the instant invention will contain from less than 1% to about 95% of the active ingredient, preferably about 10% to about 50%. Preferably, between about 10 mg and 50 mg will be administered to a child and between about 50 mg and 1000 mg will be administered to an adult. The frequency of administration will be determined by the care given based on patient responsiveness. Other effective dosages can be readily determined by one of ordinary skill in the art through routine trials establishing dose response curves.

When determining the dose of compounds to be administered which block selectin receptors, it must be kept in mind that one may not wish to completely block all of the receptors. In order

for a normal healing process to proceed, at least some of the white blood cells or neutrophils must be brought into the tissue in the areas where the wound, infection or disease state is occurring. The amount of the ligands administered as blocking agents must be adjusted carefully based on the particular needs of the patient while taking into consideration a variety of factors such as the type of disease that is being treated.

Other modes of administration will also find use with the subject invention. For instance, the ligand molecules of the invention can be formulated in suppositories and, in some cases, aerosol and intranasal compositions. For suppositories, the vehicle composition will include traditional binders and carriers such as, polyalkylene glycols, or triglycerides. Such suppositories may be formed from mixtures containing the active ingredient in the range of about 0.5% to about 10% (w/w), preferably about 1% to about 2%.

Intranasal formulations will usually include vehicles that neither cause irritation to the nasal mucosa nor significantly disturb ciliary function. Diluents such as water, aqueous saline or other known substances can be employed with the subject invention. The nasal formulations may also contain preservatives such as, but not limited to, chlorobutanol and benzalkonium chloride. A surfactant may be present to enhance absorption of the subject proteins by the nasal mucosa.

The compounds of the instant invention may also be administered as injectables. Typically, injectable compositions are prepared as liquid solutions or suspensions; solid forms suitable for solution in, or suspension in, liquid vehicles prior to injection may also be prepared. The preparation may also be emulsified or the active ingredient encapsulated in liposome vehicles.

Compounds of formula I can be mixed with compatible, pharmaceutically acceptable excipients. Suitable vehicles are, for example, water, saline, dextrose, glycerol, ethanol, or the like, and combinations thereof. In addition, if desired, the vehicle may contain minor amounts of auxiliary substances such as wetting or emulsifying agents or pH buffering agents. Actual methods of preparing such dosage forms are known, or will be apparent, to those of ordinary skill in the art. See e.g., Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pennsylvania, 17th edition, 1985. The composition or formulation to be administered will, in any event, contain a quantity of the compounds adequate to achieve the desired state in the subject being treated.

The various compounds of the present invention can be used by themselves or in combination with pharmaceutically acceptable excipient materials as described above. However, the compounds of the invention can be made as conjugates wherein they are

linked in some manner (e.g., via the R^1 moiety) to a label. By forming such conjugates, the compounds can act as biochemical delivery systems for the label so that a site of disease can be detected.

For instance, carbohydrates can be labeled by a variety of procedures, for example: esterification of hydroxyl bonds to form a structure capable of complexing directly with a radioisotope or NMR enhancer; reaction of the carbohydrate with amino diacetic acid (IDA) in organic solvent to form an N-linked glycoside derivative which would be capable of complexing with a radioisotope via the nitrogen and oxygen atoms of the IDA group; or coupling of the carbohydrate to amino acids which may be labeled directly (e.g. cysteine, tyrosine) or labeled via a bifunctional chelating agent (e.g., lysine).

Appropriate radioactive atoms would include, for example, technetium 99m (^{99m}Tc), iodine-123 (^{123}I) or indium-111 (^{111}In) for scintigraphic studies, or for nuclear magnetic resonance (NMR) imaging (also known as magnetic resonance imaging, MRI), a label such as gadolinium, manganese or iron, or a positron-emitting isotope such as iodine-124, fluorine-19, carbon-13, nitrogen-15 or oxygen-17.

Method of Synthesis (General)

Methods for introducing functionalities to a sugar are well known in the art. PCT Publication WO 97/30984 and references therein describe, inter alia, the preparation of the compounds used herein. The references also disclose how to synthesize the reactive carbon glycosides and other reactive compounds used herein. The contents of the above publications are hereby incorporated by reference for the methods of producing said reactive compounds; attachment of B groups to either of the phenyl rings by covalent bond or through an ether linker; also for the methods of introducing functionalities to the sugar (or B groups); the use of protecting groups; the use of coupling reactions to functionalize the carbon glycoside reagents; and the interconversion of alkenlyl linkers in the carbon glycoside compounds.

The compounds of the invention may also be reacted with a fluorescent probe, a multivalent compound, a ceramide, cholesterol or other lipid components, or a pharmaceutically active drug such as an anti-inflammatory drug.

Synthesis of Carbon Glycosides

The synthesis of carbon glycosides is described in PCT Publication WO 97/30984. The contents of this publication, and the references therein are hereby incorporated by reference.

The compounds of this invention and their preparation can be further understood by the following examples which illustrate some of the processes by which these compounds are prepared. The following examples are provided so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make compounds and compositions of the invention and are not intended to limit the scope of what the inventors regard as their invention. The compounds of the present invention can be prepared by methods now known or later developed. Unless indicated otherwise, parts are parts by weight, temperature is in degrees C, and pressure is at or near atmospheric.

Materials and Methods

Reagents were purchased from commercial suppliers such as Pfanstiehl Laboratories, Aldrich Chemical Company or Lancaster Synthsis Ltd. and were used without further purification unless otherwise indicated. Tetrahydrofuran (THF) and dimethylformamide (DMF) were purchased from Aldrich in sure seal bottles and used as received. 5,5' methylenedisalicylic acid was purchased from Aldrich Chemical Company or Lancaster Ltd. The analogs comprising the compound of formula I where R^1, $R^{1'}$, and R^2, are -H; R^3 and $R^{3'}$ are -OH; R^4 and $R^{4'}$ are -COOH; and $R^{2'}$ is selected from the group consisting of Y-C were isolated from

the purchased materials by column chomatography and by HPLC. All solvents were purified by using standard methods readily known to those of ordinary skill in the art unless otherwise indicated.

5

General Protocol

The reactions set forth below are done generally under a positive pressure of nitrogen or with a drying tube, at ambient temperature (unless otherwise stated), in anhydrous solvents, 10 and the reaction flasks were fitted with rubber septa for the introduction of substrates and reagents via syringe. Glassware was oven dried and/or heat dried. Analytical thin layer chromatography (TLC) was performed on glass-backed silica gel 60 F 254 plates Analtech (0.25 mm) and eluted with the appropriate 15 solvent ratios (v/v) which are noted where appropriate. The reactions were assayed by TLC and terminated as judged by the consumption of starting material.

Visualization of the TLC plates was done with a *p*-anisaldehyde spray reagent or phosphomolybdic acid reagent 20 (Aldrich Chemical 20% wt in ethanol) and activated with heat. Work-ups were typically done by doubling the reaction volume with the reaction solvent or extraction solvent and then washing with the indicated aqueous solutions using 25% by volume of the extraction volume unless otherwise indicated. Product solutions

were dried over anhydrous Na_2SO_4 prior to filtration and evaporation of the solvents under reduced pressure on a rotary evaporator and noted as solvents removed *in vacuo*.

Flash column chromatography (Still *et al.*, (1978), A.J. Org. Chem. 43:2923) was done using Baker grade flash silica fel (47-61mm) and a silica gel: crude material ratio of about 20:1 to 50:1 unless otherwise stated.

Hydrogenolysis can be done at the pressure indicated in the examples, or at ambient pressure.

All melting points are uncorrected. Microanalyses were carried out by Galbraith Laboratories, Inc., Knoxville, TN.

Formation of Allylic Ethers - General Procedure A

Formation of Doubly Substituted Disalicylates

A disalicylate (3.64 mmoles) is dissolved and is combined with a C-(chloromethallyl) glycoside (9.79 mmoles), cesium carbonate (18.3 mmoles), and tetrabutylammonium iodide (0.43 mmoles). Acetonitrile (15 ml) is then added and the mixture is stirred at room temperature for 2 days. The reaction is then diluted with ethyl acetate (150 ml) and washed with brine (3 X 50 ml). The organics are dried over anhydrous magnesium sulfate, filtered and concentrated. The residue is purified by silica gel chromatography.

Formation of Mono Substituted Disalicylates

A disalicylate (3.64 mmoles) is dissolved and is combined with a C-(chloromethallyl) glycoside (4.5 mmoles), cesium carbonate (18.3 mmoles), and tetrabutylammonium iodide (0.43 mmoles). Dimethyl formamide (15 ml) is then added and the mixture is stirred at room temperature for 2 days. The reaction is then diluted with ethyl acetate (150 ml) and washed with brine (3 X 50 ml). The organics are dried over anhydrous magnesium sulfate, filtered and concentrated. The residue is purified by silica gel chromatography.

Cope/Claisen Rearrangements - General Procedure B

An allylic ether (500 mg) is dissolved in 1,2-dichlorobenzene (5.0 ml) and heated to 180 °C for 24 hours. The resulting solution is cooled to room temperature and applied to a silica gel column. The product is isolated by direct column chromatography.

Catalytic Reduction - General Procedure C

Catalytic Hydrogenation for the Reduction of an Alkene or Removal of the Benzyl Group.

For a compound containing an alkene, 1.00 mmole equivalent is dissolved in an appropriate hydrogenation solvent suitable for the compound to be deprotected. Solvents can include but

are not restricted to, methanol, ethyl acetate, ethanol, acetic acid or combinations thereof. For example, methanol with a catalytic amount of acetic acid or ethyl acetate and methanol can be used as the hydrogenation solvent. 5% or 10% palladium on carbon (1 g for every 50 grams of starting material with the catalyst wetted with toluene under argon) is evacuated and hydrogen gas is added and the process repeated three times. The reaction is shaken or stirred for several hours until the deprotection is complete. The reaction can be done under ambient pressures or can be performed using a hydrogenation bomb at appropriate pressures (generally 10-50 psig). The reaction is terminated by removal of the excess hydrogen gas, flushing the reaction vessel with an inert atmosphere and then filtering the contents through Celite to remove the catalyst and washing the catalyst with 30% methanol in chloroform or appropriate solvent system. Concentration *in vacuo* afforded the desired compound. The product can be purified by column chromatography using Baker grade fresh silica gel (47-61mm) and a suitable solvent system. For example, 10% ethyl acetate in hexanes and then with 30% ethyl acetate in hexanes. The silica gel is eluted with methanol and checked by TLC for any product material. The solvents are removed *in vacuo* and the product dried under vacuum. The desired product is recovered.

General references on applicable transformations can be found, among other places, in:

R.C. Larock, Comprehensive Organic Transformations, ISBN 0-89573-710-8, 1989, VCH Publishers, Inc. 220 East 23rd Street, Suite 909, New York, NY 10010.

Jerry March, Advanced Organic Chemistry, 3rd Edition, c1985, ISBN 0-471-88841-9, John Wiley & Sons Publishers, New York USA.

H. O. House, Modern Synthetic Reactions, c1972, ISBN 0-8053-4501-9, The Benjamin/Cummings Publishing Company, Menlo Park, California, USA.

F.A. Carey and R.J. Sundberg, Advanced Organic Chemistry Parts A & B, 2nd Edition, c1983, ISBN 0-306-41199-7, Plenum Press, a division of Plenum Publishing Corporation, 233 Spring Street, New York, N.Y. 10013, USA.

General Procedure D: Hydrolysis of Ester Groups

An ester (2.0 mmoles) is dissolved in methanol (2.0 ml) and 2N NaOH (2.0 ml) is added. If the reaction involves 2.0 mmoles of a di-salicylate, 4.0 ml of methanol and 4.0 ml of 2N NaOH is required. The reaction is stirred at room temperature for 24 hours. The reaction is then acidified using Dowex acid ion exchange resin. The mixture is filtered and the product is isolated on concentration of the filtrate.

General Procedure E: Formation of Sodium Salts

A carboxylic acid (0.5 mmoles) is dissolved in water (5 ml) and Dowex sodium ion exchange resin is added. The mixture is stirred until the pH reaches 8 as measured by pH paper. The reaction is filtered and the water is removed by lyophilization to give the desired product.

This procedure is directly applicable to any and all of the carboxylic acid analogs disclosed in the present invention.

Other General Procedures

One of ordinary skill in the art will appreciate and understand the following general procedures as they are used in the art to prepare novel compounds from the invention. These and other objects, advantages and features of the following procedures will become apparent to those persons skilled in the art upon reading the details of the synthesis, structure, formulation and usage as more fully set forth below. One of skill in the art will further recognize that the compounds of the present invention can be prepared in a number of ways. The following procedures show one preferred method of preparing the compounds of the present invention.

General Procedure F: Conversion of Olefins to Ketones

An olefin (1.58 mmoles) is dissolved in acetone (7.2 ml) and water (0.8 ml) is added followed by a solution of OsO_4 in acetone (1M, 0.16 ml). Following the addition of $NaIO_4$ (15.85 mmoles), the reaction is stirred at room temperature for 3 hours and diluted with water (40 ml). (If multiple olefins are present on a single starting material, the amounts of OsO_4 and NaIO4 should be calculated based upon olefin equivalents.) The organics are extracted with ethyl acetate (3 X 20 ml). The organics are then washed with saturated aqueous $Na_2S_2O_3$ (4 X 10 ml) and brine (10 ml). The organics are then dried over anhydrous $MgSO_4$, filtered and concentrated. The residue is purified on silica gel.

General Procedure G: Protection of Ketones

A ketone (0.33 mmoles) is dissolved in methanol (2.0 ml) and camphor sulfonic acid (0.03 mmole) is added. The reaction is stirred at room temperature until complete by TLC. The solvent is then removed and the residue is purified on silica gel to give a dimethyl ketal. Since under the conditions described above an alpha-C-glycoside beta to the carbonyl group will undergo isomerization to a beta-C-glycoside, excessive reaction time may be detrimental to the reaction yield.

General Procedure H: Deprotection of Ketones

A dimethyl ketal (1.0 mmole) is dissolved in tetrahydrofuran (10 ml) and 1N HCl (10 ml) is added. The reaction is stirred at room temperature until complete (by TLC). The product is then extracted with ethyl acetate (3 X 15 ml). The organics are washed with saturated aqueous sodium bicarbonate (3 X 10 ml) and brine (10 ml). The organics are then dried over anhydrous magnesium sulfate, filtered and concentrated. The residue is purified by silica gel chromatography to give the desired ketone. Because under these conditions an alpha-C-glycoside beta to the carbonyl group will undergo isomerization to a beta-C-glycoside, excessive reaction time may be detrimental to the reaction yield.

General Procedure I: Protection of Phenolic Hydroxyl Groups

A phenol (1.23 mmoles) is dissolved in acetic anhydride (3 ml) and pyridine (3 ml) is added. The reaction is stirred at room temperature for 24 hours. The reaction is then diluted with ethyl acetate (50 ml). The mixture is washed with 1N HCl (3 X 5 ml), saturated aqueous sodium bicarbonate (3 X 5 ml), water (5 ml), saturated aqueous copper sulfate (3 X 5 ml) and brine (5 ml). The organics are dried over anhydrous magnesium sulfate, filtered and concentrated to dryness giving the desired acetylated product.

General Procedure J: Deprotection of Phenolic Hydroxyl Groups

An acylated phenol (1 mmole) is dissolved in anhydrous ethanol (10 ml) and a solution of sodium ethoxide in ethanol (21 wt. %, Aldrich, 1ml) is added. The reaction is stirred until complete by TLC and quenched with Dowex acid ion exchange resin. The mixture is filtered and the residue is concentrated giving the desired phenol.

General Procedure K: Formation of Silyl Ethers

A polyhydroxylated compound (1 mmole) is dissolved in THF (10 ml) and tert-butyl dimethylsilyl chloride (1.1 mmole for each hydroxyl group) is added followed by imidazole (1.15 mmole for each hydroxyl group). The reaction is stirred until it is complete by TLC. Upon completion, the solvent is removed and the residue is diluted with ethyl acetate. The resulting mixture is washed with 1N HCl (3X), saturated aqueous sodium bicarbonate (3X) and brine (1X). The organic phase is dried over anhydrous magnesium sulfate, filtered and concentrated. The product is purified by silica gel chromatography.

General Procedure L: Formation of Olefins

Methyltriphenylphosphonium bromide (1.2 mmole) is dissolved in THF (10 ml) and added to a suspension of sodium hydride (1.1

mmole) in THF (10 ml) at 0°C under argon. The mixture is stirred until no more gas is liberated. A solution of a ketone (1 mmole) in THF (10 ml) is then added to the dark red solution and the reaction is stirred at 0°C until complete by TLC. The reaction is quenched with saturated aqueous ammonium chloride (10 ml) and diluted with ethyl acetate (100 ml). The organics are washed with 1N HCl (3 X 10 ml), saturated aqueous sodium bicarbonate (3 X 10 ml) and brine (10 ml). The organic phase is then dried over anhydrous magnesium sulfate, filtered and concentrated. The product is purified by silica gel chromatography.

General Procedure M: Removal of Silyl Groups

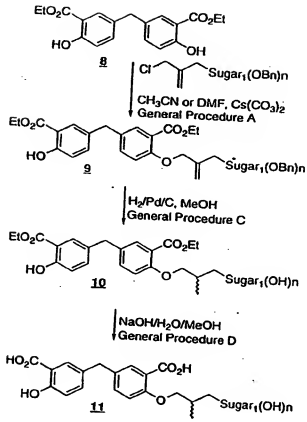
A silyl ether (1 mmole) is dissolved in THF (10 ml) and tetrabutyl ammonium fluoride (1M in THF, 1.1 mmole for each silyl ether) is added. The reaction is stirred at 0°C until complete by TLC after which, it is filtered through a 1 inch plug of silica gel (ethyl acetate). The solvent is removed and the product is purified by silica gel chromatography.

In all cases, every molecule comprising at least one suitable functional group can be employed as substrate to react with the activated carbon glycosides/heteroatom glycosides of the present invention.

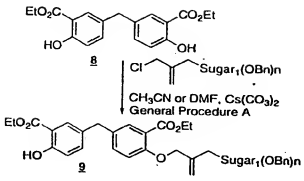
The common transformations described above are generally known to those skilled in the art and the methodologies described, and equivalent methodologies are available in advanced organic chemistry textbooks, and references cited therein.

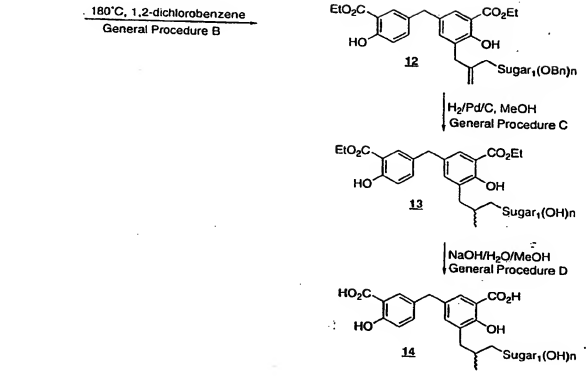
Various compounds of the invention can be made using the general and specific synthesis schemes and examples described below. However, those skilled in the art will recognize variations thereof which are intended to be encompassed by the present invention. The compounds of the present invention can be prepared in a number of ways. The following schemes show one preferred method of preparing various compounds of the present invention.

Scheme 1

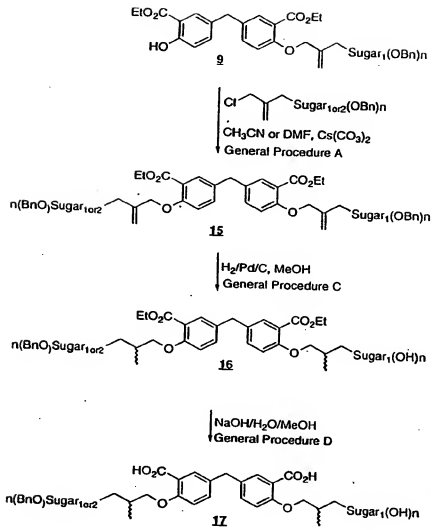

EtO2C
CO2Et
HO
OH
8
Cl
Sugar1(OBn)n
CH3CN or DMF, Cs(CO3)2
General Procedure A
9
H2/Pd/C, MeOH
General Procedure C
10
Sugar1(OH)n
NaOH/H2O/MeOH
General Procedure D
HO2C
CO2H
11

Scheme 2

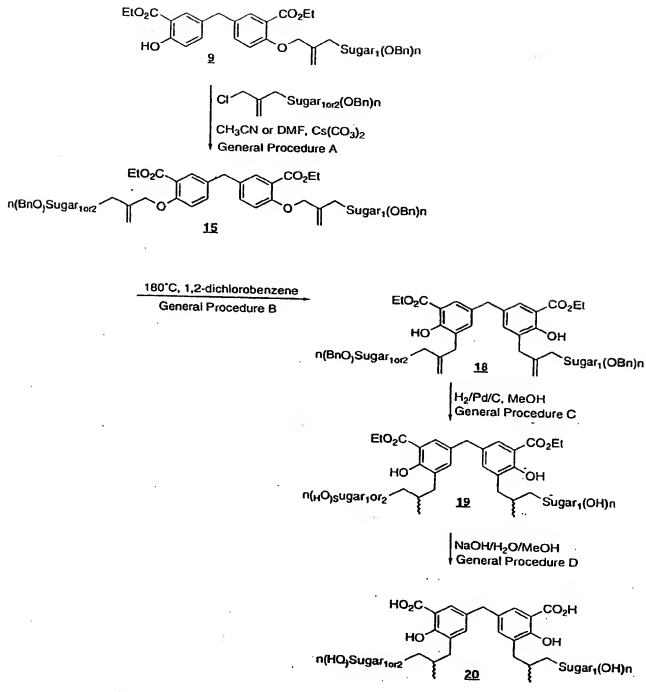

EtO2C
CO2Et
HO
OH
8
Cl
Sugar1(OBn)n
CH3CN or DMF, Cs(CO3)2
General Procedure A
EtO2C
CO2Et
HO
O
Sugar1(OBn)n
9


180°C, 1,2-dichlorobenzene
General Procedure B
EtO2C
CO2Et
HO
OH
12
Sugar1(OBn)n
H2/Pd/C, MeOH
General Procedure C
EtO2C
CO2Et
HO
OH
13
Sugar1(OH)n
NaOH/H2O/MeOH
General Procedure D
HO2C
CO2H
HO
OH
14
Sugar1(OH)n

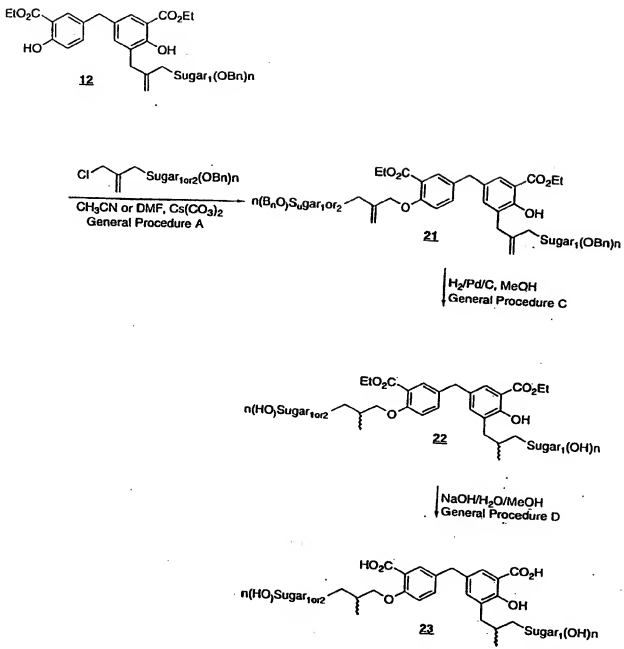
Scheme 3


EtO2C
CO2Et
HO
O
Sugar1(OBn)n
9
Cl
Sugar1or2(OBn)n
CH3CN or DMF, Cs(CO3)2
General Procedure A
n(BnO)Sugar1or2
15
H2/Pd/C, MeOH
General Procedure C
Sugar1(OH)n
16
NaOH/H2O/MeOH
General Procedure D
HO2C
CO2H
17

Scheme 4


EtO2C
CO2Et
HO
Sugar1(OBn)n
9
Cl
Sugar1or2(OBn)n
CH3CN or DMF, Cs(CO3)2
General Procedure A
n(BnO)Sugar1or2
15
180°C, 1,2-dichlorobenzene
General Procedure B
OH
18
H2/Pd/C, MeOH
General Procedure C
n(HO)Sugar1or2
19
Sugar1(OH)n
NaOH/H2O/MeOH
General Procedure D
HO2C
CO2H
n(HO)Sugar1or2
20

Scheme 5


EtO2C
CO2Et
HO
OH
Sugar1(OBn)n
12
Cl
Sugar1or2(OBn)n
CH3CN or DMF, Cs(CO3)2
General Procedure A
n(BnO)Sugar1or2
21
H2/Pd/C, MeOH
General Procedure C
n(HO)Sugar1or2
22
Sugar1(OH)n
NaOH/H2O/MeOH
General Procedure D
HO2C
CO2H
23

EXAMPLES

Generation of Compounds

General Experimental Procedures:

One of ordinary skill in the art will appreciate and understand the following general examples as they are used in the art to prepare novel compounds from the invention. The "mmole equivalent" refers to the reaction substrate to be functionalized by the reaction with a reagent per position to be alkylated. The skilled artisan using standard reaction conditions can accomplish additional functional group transformations. For example, the transformation of allylic halides into allylic amines can be via the allylic azide with reduction of the azide to the amine with triphenylphosphine in water. The amine is then available for amide bond formation.

The compounds are referred to by numbers, which correspond to the numbers in the general structures in Schemes 1-5. The letters next to the numbers (a, b, c etc.) refer to the tables and indicate which sugar is present in the C-Glycoside represented in the Schemes generically by the term "$sugar_1(OH)_n$" or "$sugar_1(OBn)_n$" (depending on whether it is still protected or not). For example, compound **9a** (see below) was synthesized according to general procedure A shown in scheme 1. The compound has the general structure indicated in scheme 1 as **9**

and the "$Sugar_1$ $(OBn)_n$" corresponds to a fucose as indicated in the table.

Compounds Prepared in Scheme 1

	Sugar 1
9a	Fucose
9b	Glucose
10a	Fucose
10b	Glucose
11a	Fucose
11b	Glucose

Compound **9a** was prepared according to General Procedure A utilizing the following reagents and quantities: Ethyl salicylate dimer (5.81 mmoles), Tri-O-benzyl fucose allyl chloride (3.00 mmoles), cesium carbonate (6.31 mmoles), tetrabutyl ammonium iodide (0.84 mmoles), dimethyl formamide (30 ml). Silica gel chromatography solvent: 10% ethyl acetate/hexane to 50% ethyl acetate/hexane. The reaction's yield was 1.35g of **9a** and 0.64 g of **15a**.

Compound **9b** was prepared according to General Procedure A utilizing the following reagents and quantities: Ethyl salicylate

dimer (120 mg), Tetra-O-benzyl glucose allyl chloride (192 mg), cesium carbonate (133 mg), tetrabutyl ammonium iodide (26 mg), dimethyl formamide (1.7 ml). Silica gel chromatography solvent: 15% ethyl acetate/hexane to 30% ethyl acetate/hexane. The reaction's yield was 82 mg of **9b** and 71 mg of **15c**.

Compound **10a** was prepared according to General Procedure C utilizing the following reagents and quantities: Compound 9a (0.24 g), 10% Pd/C (0.13 g), MeOH (50 ml), ethyl acetate (3 ml). Silica gel chromatography solvent: 5% MeOH/$CHCl_3$. The reaction's yield was 60%.

Compound **10b** was prepared according to General Procedure C utilizing the following reagents and quantities: Compound 9b (250 mg), 10% Pd/C (140 mg), MeOH (36 ml), ethyl acetate (15 ml). Silica gel chromatography solvent: 5% MeOH/CHCl3 to 10% MeOH/$CHCl_3$. The reaction's yield was 67%.

Compound **11a** was prepared according to General Procedure D utilizing the following reagents and quantities: Compound 10a (300 mg), 2N NaOH (1.6 ml), MeOH (3.0 ml). No purification was necessary. The reaction's yield was 100%.

Compound **11b** was prepared according to General Procedure D utilizing the following reagents and quantities: Compound 10b (216

mg), 2N NaOH (1.2 ml), MeOH (2.3 ml). No purification was necessary. The reaction's yield was 88%.

Compounds Prepared in Scheme 2

	Sugar 1
12a	Fucose
12b	Glucose
13a	Fucose
13b	Glucose
14a	Fucose
14b	Glucose

Compound **12a** was prepared according to General Procedure B utilizing the following reagents and quantities: Compound 11a (0.51 g), 1,2-dichlorobenzene (5.0 ml). Silica gel chromatography solvent: 10% ethyl acetate/hexane. The reaction's yield was 50%.

Compound **12b** was prepared according to General Procedure B utilizing the following reagents and quantities: Compound 11b (0.50 g), 1,2-dichlorobenzene (5.0 ml). Silica gel chromatography solvent: 15% ethyl acetate/hexane. The reaction's yield was 46%.

Compound **13a** was prepared according to General Procedure C utilizing the following reagents and quantities: Compound 12a (0.61 g), 10% Pd/C (0.15 g), MeOH (27.0 ml). Silica gel

chromatography solvent: Ethyl acetate. The reaction's yield was 68%.

Compound **13b** was prepared according to General Procedure C utilizing the following reagents and quantities: Compound 12b (0.46 g), 10% Pd/C (0.11 g), MeOH (16.0 ml), ethyl acetate (4 ml). No purification was necessary. The reaction's yield was 94%.

Compound **14a** was prepared according to General Procedure D utilizing the following reagents and quantities: Compound 13a (168 mg), 2N NaOH (0.92 ml), MeOH (1.84 ml). No purification was necessary. The reaction's yield was 100%.

Compound **14b** was prepared according to General Procedure D utilizing the following reagents and quantities: Compound 13b (167 mg), 2N NaOH (0.89 ml), MeOH (1.79 ml). No purification was necessary. The reaction's yield was 99%.

Compounds Prepared in Scheme 3

	Sugar1	Sugar2
15a	Fucose	Fucose
15b	Fucose	Glucose
15c	Glucose	Glucose
16a	Fucose	Fucose
16b	Fucose	Glucose
16c	Glucose	Glucose
17a	Fucose	Fucose
17b	Fucose	Glucose
17c	Glucose	Glucose

Compound **15a** was prepared according to General Procedure A utilizing the following reagents and quantities: Ethyl salicylate dimer (5.81 mmoles), Tri-O-benzyl fucose allyl chloride (3.00 mmoles), cesium carbonate (6.31 mmoles), tetrabutyl ammonium iodide (0.84 mmoles), dimethyl formamide (30 ml). Silica gel chromatography solvent: 10% ethyl acetate/hexane to 50% ethyl acetate/hexane. The reaction's yield was 1.35g of **9a** and 0.64 g of **15a**.

Compound **15b** was prepared according to General Procedure A utilizing the following reagents and quantities: Compound 9b (0.98 mmole), Tri-O-benzyl fucose allyl chloride (2.07 mmoles), cesium carbonate (1.50 mmoles), tetrabutyl ammonium iodide (0.67 mmoles), acetonitrile (5 ml), dimethylformamide (2 ml). Silica

gel chromatography solvent: 15% ethyl acetate/hexane. The reaction's yield was 85%.

Compound **15c** was prepared according to General Procedure A utilizing the following reagents and quantities: Ethyl salicylate dimer (120 mg), Tetra-O-benzyl glucose allyl chloride (192 mg), cesium carbonate (133 mg), tetrabutyl ammonium iodide (26 mg), dimethyl formamide (1.7 ml). Silica gel chromatography solvent: 15% ethyl acetate/hexane to 30% ethyl acetate/hexane. The reaction's yield was 82 mg of **9b** and 71 mg of **15c**.

Compound **16a** was prepared according to General Procedure C utilizing the following reagents and quantities: Compound 15a (72 mg), 10% Pd/C (25 mg), MeOH (20 ml). Silica gel chromatography solvent: 5% MeOH/$CHCl_3$. The reaction's yield was 55%.

Compound **16b** was prepared according to General Procedure C utilizing the following reagents and quantities: Compound 15b (0.31 g), 10% Pd/C (0.16g), MeOH (35 ml), ethyl acetate (6 ml). Silica gel chromatography solvent: 5% MeOH/$CHCl_3$. The reaction's yield was 35%.

Compound **16c** was prepared according to General Procedure C utilizing the following reagents and quantities: Compound 15c (1.16 g), 10% Pd/C (0.35 g), MeOH (35 ml), ethyl acetate (15 ml).

Silica gel chromatography solvent: 5% MeOH/$CHCl_3$ to 10% MeOH/$CHCl_3$. The reaction's yield was 27%.

Compound **17a** was prepared according to General Procedure D utilizing the following reagents and quantities: Compound 16a (0.25 mmoles), 2N NaOH (0.8 ml), MeOH (1.6 ml). No purification was necessary. The reaction's yield was 87%.

Compound **17b** was prepared according to General Procedure D utilizing the following reagents and quantities: Compound 16b (120 mg), 2N NaOH (0.5 ml), MeOH (1.0 ml). No purification was necessary. The reaction's yield was 100%.

Compound **17c** was prepared according to General Procedure D utilizing the following reagents and quantities: Compound 16c (120 mg), 2N NaOH (0.5 ml), MeOH (1.0 ml). No purification was necessary. The reaction's yield was 88%.

Compounds Prepared in Scheme 4

	Sugar1	Sugar2
18a	Fucose	Fucose
18b	Fucose	Glucose
18c	Glucose	Glucose
19a	Fucose	Fucose
19b	Fucose	Glucose
19c	Glucose	Glucose
20a	Fucose	Fucose
20b	Fucose	Glucose
20c	Glucose	Glucose

Compound **18a** was prepared according to General Procedure B utilizing the following reagents and quantities: Compound 15a (0.50 g), 1,2-dichlorobenzene (5.0 ml). Silica gel chromatography solvent: 20% ethyl acetate/hexane. The reaction's yield was 50%.

Compound **18b** was prepared according to General Procedure B utilizing the following reagents and quantities: Compound 15b (1.61 g), 1,2-dichlorobenzene (16 ml). Silica gel chromatography solvent: 10% ethyl acetate/hexane. The reaction's yield was 45%.

Compound **18c** was prepared according to General Procedure B utilizing the following reagents and quantities: Compound 15c (1.60 g), 1,2-dichlorobenzene (16 ml). Silica gel chromatography solvent: 10% ethyl acetate/hexane. The reaction's yield was 32%.

Compound **19a** was prepared according to General Procedure C utilizing the following reagents and quantities: Compound 18a (0.80 g), 10% Pd/C (0.20 g), MeOH (15.0 ml), ethyl acetate (3 ml). No purification was necessary. The reaction's yield was 64%.

Compound **19b** was prepared according to General Procedure C utilizing the following reagents and quantities: Compound 18b (1.34 g), 10% Pd/C, MeOH (60 ml). No purification was necessary. The reaction's yield was 67%.

Compound **19c** was prepared according to General Procedure C utilizing the following reagents and quantities: Compound 18c (0.51 g), 10% Pd/C (0.51 g), MeOH (15.0 ml), ethyl acetate (5 ml). No purification was necessary. The reaction's yield was 83%.

Compound **20a** was prepared according to General Procedure D utilizing the following reagents and quantities: Compound 19a (189 mg), 2N NaOH (0.75 ml), MeOH (1.49 ml). No purification was necessary. The reaction's yield was 94%.

Compound **20b** was prepared according to General Procedure D utilizing the following reagents and quantities: Compound 19b (217 mg), 2N NaOH (0.85 ml), MeOH (1.70 ml). No purification was necessary. The reaction's yield was 100%.

Compound **20c** was prepared according to General Procedure D utilizing the following reagents and quantities: Compound 19c (145 mg), 2N NaOH (0.56 ml), MeOH (1.12 ml). No purification was necessary. The reaction's yield was 97%.

Compounds Prepared in Scheme 5

	Sugar1	Sugar2
21a	Fucose	Fucose
21b	Fucose	Glucose
21c	Glucose	Fucose
21d	Glucose	Glucose
22a	Fucose	Fucose
22b	Fucose	Glucose
22c	Glucose	Fucose
22d	Glucose	Glucose
23a	Fucose	Fucose
23b	Fucose	Glucose
23c	Glucose	Fucose
23d	Glucose	Glucose

Compound **21a** was prepared according to General Procedure A utilizing the following reagents and quantities: compound 12a (1.10 mmoles), Tri-O-benzyl fucose allyl chloride (1.18 mmoles), cesium carbonate (1.12 mmoles), tetrabutyl ammonium iodide (0.54 mmoles), dimethyl formamide (6 ml). Silica gel chromatography solvent: 5% ethyl acetate/hexane to 31 % ethyl acetate/hexane. The reaction's yield was 49%.

Compound **21b** was prepared according to General Procedure A utilizing the following reagents and quantities: compound 12a (1.22 mmoles), Tetra-O-benzyl glucose allyl chloride (1.28 mmoles), cesium carbonate (1.27 mmoles), tetrabutyl ammonium iodide (0.30 mmoles), dimethyl formamide (9 ml). Silica gel chromatography solvent: 15% ethyl acetate/hexane to 30% ethyl acetate/hexane. The reaction's yield was 65%.

Compound **21c** was prepared according to General Procedure A utilizing the following reagents and quantities: compound 12b (0.89 mmoles), Tri-O-benzyl fucose allyl chloride (0.95 mmoles), cesium carbonate (0.95 mmoles), tetrabutyl ammonium iodide (0.20 mmoles), dimethyl formamide (10 ml). Silica gel chromatography solvent: 15% ethyl acetate/hexane to 20% ethyl acetate/hexane. The reaction's yield was 52%.

Compound **21d** was prepared according to General Procedure A utilizing the following reagents and quantities: compound 12b (0.42 mmoles), Tetra-O-benzyl glucose allyl chloride (0.47 mmoles), cesium carbonate (0.48 mmoles), tetrabutyl ammonium iodide (0.16 mmoles), dimethyl formamide (5 ml). Silica gel chromatography solvent: 10% ethyl acetate/hexane to 30% ethyl acetate/hexane. The yield was not determined.

Compound **22a** was prepared according to General Procedure C utilizing the following reagents and quantities: Compound 21a (630 mg), 10% Pd/C (210 mg), MeOH (20 ml), ethyl acetate (20 ml). Silica gel chromatography solvent: 5% MeOH/$CHCl_3$ to 30% MeOH/$CHCl_3$. The reaction's yield was 24%.

Compound **22b** was prepared according to General Procedure C utilizing the following reagents and quantities: Compound 21b (1.11 g), 10% Pd/C (0.25 g), MeOH (10 ml), ethyl acetate (25 ml). Silica gel chromatography solvent: 10% MeOH/$CHCl_3$ to 20% MeOH/$CHCl_3$. The reaction's yield was 28%.

Compound **22c** was prepared according to General Procedure C utilizing the following reagents and quantities: Compound 21c (0.70 g) 10% Pd/C (0.28 g), MeOH (30 ml), ethyl acetate (20 ml). Silica gel chromatography solvent: 15% MeOH/$CHCl_3$ to 30% MeOH/$CHCl_3$. The yield was not determined.

Compound **22d** was prepared according to General Procedure C utilizing the following reagents and quantities: Compound 21d (0.55 g), 10% Pd/C (0.23 g), MeOH (20 ml), ethyl acetate (20 ml). Silica gel chromatography solvent: 0% MeOH/$CHCl_3$ to 30% MeOH/$CHCl_3$. The reaction's yield was 35%.

Compound **23a** was prepared according to General Procedure D utilizing the following reagents and quantities: Compound 22a (0.17 mmoles), 2N NaOH (0.5 ml), MeOH (1.0 ml). No purification was necessary. The reaction's yield was 100%.

Compound **23b** was prepared according to General Procedure D utilizing the following reagents and quantities: Compound 22b (0.15 mmoles), 2N NaOH (0.5 ml), MeOH (1.0 ml). No purification was necessary. The reaction's yield was 95%.

Compound **23c** was prepared according to General Procedure D utilizing the following reagents and quantities: Compound 22c (0.07 mmoles), 2N NaOH (0.3 ml), MeOH (1.0 ml). No purification was necessary. The yield was not determined.

Compound **23d** was prepared according to General Procedure D utilizing the following reagents and quantities: Compound 22d (66 mg), 2N NaOH (0.5 ml), MeOH (1.0 ml). The yield was not determined.

Example A - The Selectin Rolling Assay And The Effect Of Disalicylate Analogs On Neutrophil Attachment To Selectins

Neutrophils roll along vessel walls, attach to the vessel, and then migrate into tissues at sites of acute inflammation. Selectins mediate the rolling and attachment of neutrophils.

Thus, inhibition of neutrophil attachment to selectins indicates activity as a cell adhesion inhibitor and as an anti-inflammatory.

Adhesion of leukocytes or HL-60 cells to P- and E-selectin under flow conditions in the presence of the compound to be assayed is measured according to the methods described by Patel, *et al.* J. Clin. Invest. (1995) 96:1887-1896.

Adhesion of leukocytes or HL-60 cells to P- and E-selectin under flow conditions is assayed as follows. Fluid shear stresses present in the microvasculature are simulated in a parallel-plate flow chamber. Jones, *et al.*, Biophys. J. (1994) 65:1560-1569; Moor, *et al.*, J. Cell. Biol. (1995) 128:661-671. Leukocytes (10^6/ml) in HBSS/0.5% HSA are perfused through the chamber at the desired wall shear stress. Leukocytes rolling is allowed to equilibrate for 4 min. on E- or P-selectin expressing CHO cells or IL-1β, TNFα or IL-4 stimulated human endothelial cells and for 8 min. on selectin-coated plastic before data acquisition. Experiments comparing control and test leukocytes are performed in parallel chambers on the same culture dish. Leukocyte interactions are visualized with a x40 objective (field of view of 0.032 mm^2) using phase-contrast video microscopy. Interactions are quantified using a computer imaging system (Sun Microsystem, Mountain View, CA; Inovision, Durham, NC). The number of adherent or rolling leukocytes is

measured by digitizing image frames and determining the number of cells that are firmly adherent or rolling as described by Jones, *et al.* supra. Detachment of leukocytes is determined by allowing leukocytes to adhere to the surface under static conditions then initiating flow at a wall shear stress of 1 dyn/cm^2. The wall shear stress is increased incrementally every 30s and the number of leukocytes remaining adherent is determined. All experiments are performed at 22°C unless indicated otherwise. In certain experiments cells are preincubated for 10 min with inhibitor and rolling is assayed in the continuous presence of the inhibitor. Results of these experiments are presented in Tables A-G.

Example B - Identification of Compounds Which Act as E, L and/or P-Selectin Ligands Using Recombinantly Produced Receptor COS cells Selectin Cell-Based Assay

A complete cDNA for the E, L and/or P-selectin receptor was obtained by PCR starting with total RNA isolated from IL-1 stimulated human umbilical vein endothelium. The resulting cDNA was inserted into the CDM8 plasmid (see Aruffo *et al.*, Proc. Natl. Acad. Sci. USA (1987) 84:8573) and the plasmid amplified in *E. coli*. Plasmid DNA from individual colonies was isolated and used to transfect COS cells. Positive plasmids were selected by their ability to generate COS cells that support HL-

60 cell adhesion. DNA sequencing positively identified one of these clones as encoding for E, L and/or P-selectin (Bevilacqua *et al.*, Science, (1989) 243:1160; Polte *et al.*, Nucleic Acids Res. (1990) 18:1083; Hession *et al.*, Proc. Natl. Acad. Sci. USA (1990) 87:1673). These publications are incorporated herein by reference for their disclosure of E-selectin and genetic material coding for its production. The complete nucleotide sequence of the E-selectin cDNA and predicted amino acid sequence of the E-selectin protein are given in the above cited article by Bevilacqua *et al.*, which DNA and amino acid sequences are incorporated herein by reference (see also published PCT patent application WO90/13300 which was published November 15, 1990, which is incorporated herein by reference).

COS cells, expressing membrane-bound E, L and/or P-selectin, were metabolically radiolabeled with T_2PO_4 (tritiated phosphoric acid). These labeled cells can be used as probes in two assay systems to screen for recognition of the compounds of formula I. More specifically, compounds of formula I may be adsorbed to the bottoms of PVC microliter wells or resolved on TLC plates. In either assay the compounds may be probed for their ability to support adhesion of E, L and/or P-selectin-transfected COS cells, untransfected COS cells, or COS cells transfected with a plasmid containing an irrelevant cDNA, under conditions of controlled detachment force (see Swank-Hill *et*

al., Anal. Biochem. (1987) 183:27; and Blackburn *et al.*, J. Biol. Chem. (1986) 261:2873 each of which is incorporated herein by reference to disclose the details of such assaying methodology).

Chinese Hamster Ovary (CHO) cells Selectin Cell-Based Assay

Chinese Hamster Ovary (CHO) cells were transfected by electroporation with plasmids CDM8-E-selectin or CDM8-P-selectin (containing the cDNA for the full-length E- or P-selectin, respectively) and pSVneo, and selected by resistance to neomycin. Individual cells were cloned and/or selected by flow cytometry for selectin expression using monoclonal antibodies to E- or P-selectin.

Cell plates for testing the compounds of the invention were prepared as follows:

Ninety-six well Corning plates were coated with 0.2% gelatin. Plates were seeded with either $5x10^4$ cells/well or $3x10^4$ cells/well and grown for either 2 or 3 days. Cells seeded at lower density on Friday will be ready for assay on Monday. The monolayer was rinsed with PBS. Then the cells were fixed with 50µl of 0.5% Paraformaldehyde for 20 minutes. The plates were then rinsed with PBS and blocked with 1% BSA/PBS, 100 µl/well, 20-30 minutes at room temperature. The plates are washed with PBS just before adding the compounds to be assayed.

HL-60 Cell Preparation Was As Follows:

HL-60 cells were counted and $7.5x10^6$ cells/plate were removed. The cells were washed by filling a 50 ml centrifuge tube with PBS (no more than 20 ml of cells/50 ml tube). The cells were resuspended at $2x10^6$/ml (7.5 ml for 2 plates). Then BCECF-AM [10 mM stock] at 5µM, 1/2000 dilution was added. The cell preparation was incubated for 30 minutes at 37°C. The tube was filled with PBS to wash, then it was centrifuged as before, and decanted. The cells were pelleted at 1000 rpm for 10 min. The cells were resuspended at $1.5x10^6$cells/ml (10 ml).

Compounds were tested at various concentrations, beginning with a 1:5 dilution. 40µl of compound is added to quadruplicate wells, followed by 40µl of cells. The suspension is rotated at 50 rpm for 20 minutes at room temperature. Unbound cells are removed or flicked. The mixture is washed 2X with PBS. Then 75 µl of lysis buffer (100ml TRIS, pH 9.5, 2% Triton S100) is added. The control is 10µl of labeled cells mixed with 65µl of lysis buffer. The excitation fluorescence is read at 485 nm, the emission fluorescence is read at 530 nm with a gain of 60 on the cytofluor. A decrease in fluorescence indicates inhibition of adhesion of the cells to the monolayer.

Results

Results for these experiments are also presented in Tables A-G.

Table A

The compound of Formula I wherein R^1, $R^{1'}$, R^2, $R^{2'}$, R^3, $R^{3'}$, R^6, and $R^{6'}$ are -H; R^7 is -OH; R^4 and $R^{4'}$ are -$COOR^{11}$; and R^5 is -$W((CH_2)_m-(CHR^9)_q-(CH_2)_m-A)_t$; -W is -O-; m is 1; q is 1; R^9 is -CH_3; t is 1; and R^{11} and -A are as in the table.

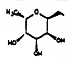
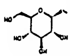
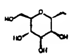
-A	R^{11}	E-COS (IC_{50}, µM)	E-CHO Rolling (IC_{50}, µM)	P-CHO (IC_{50}, µM)	P-CHO Rolling (IC_{50}, µM)	L(cv) Rolling (IC_{50}, µM)	L(rc) Rolling (IC_{50}, µM)
	-CH_2-CH_3	407, 655	nt	1039, 1382	nt		I
	-H	> 5000		2853, >5000, >2500	>2500	>2500	
	-CH_2-CH_3	822, 1324	nt	799, 1132	nt		
	-H	545, 2485		1652, 1065	2500@5m		
	-CH_2-CH_3	2789, 834		3124, 1291	100@2m		
	Na^+	2224, 2406	1000	978, 2316	1000@5m		

Table B

The compound of formula I wherein R^1, R^2, R^3, R^4, R^5, and R^6 are -H; R^7 and R^8 are =OH; R^9 and R^{10} are =COOH; and R^{11} is -W-((CH$_2$)$_m$-Y-(CHR^9)$_q$-(CH$_2$)$_m$-A)$_t$: W is a covalent bond; m is 1; q is 1; R^9 is -CH$_2$; t is 1; and R^{11} and -A are as in the table.

-A	R^{11}	E-COS (IC_{50} µM)	E-CHO Rolling (IC_{50} µM)	P-CHO (IC_{50} µM)	P-CHO Rolling (IC_{50} µM)	L(cy) Rolling (IC_{50} µM)	L(cy) Rolling (IC_{50} µM)
	-CH_2-CH_3	>5000	ni	2939, 1678	2500@5m		
	-H	>5000	ni	1272, 482, 467, 713	2500@5m	1000	
	-CH_2-CH_3	1503, 377	ni	1647, 733	ni		
	-H	>5000	ni	821, 2653, 1253	ni		

Table C

The compound of formula I wherein R^1, $R^{1'}$, R^2, $R^{2'}$, R^3, $R^{3'}$, R^4, and $R^{4'}$ are -H; R^5 and $R^{5'}$ are -W-$(CH_2)_q$-$(CHR^9)_n$-$(CH_2)_m$-Ar; R^6 and $R^{6'}$ are -$COOR^{11}$; -W is -O-; m is 1; q is 1; R is -CH_2-; t is 1; and R^{11} and -A are as in the table.

A	R^{11}	B-COS (IC_{50}, μM)	B-CHO Rating (IC_{50}, μM)	P-CHO (IC_{50}, μM)	P-CHO Rating (IC_{50}, μM)	L(ev) Rating (IC_{50}, μM)	L(rv) Rating (IC_{50}, μM)
	$-CH_2CH_3$	>5000	m	145, 2357	m		
	-H	>5000, 4868	m	732, 845	m	>5000	
	$-CH_2CH_3$	>5000	m	859, 245	m		
	-H	>5000	m	1744, 765	m		

Table D

The compound of Formula I wherein R^1, R^2, R^3, R^5, R^6, and R^8 are -H; R^4 and R^7 are -W-$(CH_2)_m$-CHR^9-$(CH_2)_n$-A_1; R^9 and R^{10} are -OH; and R^{11} and R^{12} are -$COOR^{13}$; -W is a covalent bond; m is 1; q is 1; R^{13} is -CH_2-; t is 1; and R^{11} and -A are as in the table.

R_3	R	E-COS (IC_{50} µM)	E-CHO Rolling (IC_{50} µM)	P-CHO (IC_{50} µM)	P-CHO Rolling (IC_{50} µM)	L(pr) Rolling (IC_{50} µM)	L(er) Rolling (IC_{50} µM)
	$-CH_2-CH_3$	>5000	ni	745, <40	100@3m	2500	
	-H	3002, 3372	ni	728, 350	1000@3m	2500	
	$-CH_2-CH_3$	4820, >5000	ni	634, 89	10	10	1
	Na^+	3104, 3313	ni	763, 239	>2500		

Table E

The compound of Formula I wherein R^1, R^2, R^3, R^5, R^6, R^8, and R^{12} are -H; R^4 is -W-$(CH_2)_m$-CHR^9-$(CH_2)_n$-A_1; R^7 is -W-$(CH_2)_m$-CHR^9-$(CH_2)_n$-A_1; R^9 and R^{10} are -$COOR^{13}$; -W is -O-; m is 1; q is 1; R^{13} is -CH_2-; t is 1; and R^{11}, -A, and -A_1 are as in the table.

-A	-A_1	R^{11}	E-COS (IC_{50} µM)	E-CHO Rolling (IC_{50} µM)	P-CHO (IC_{50} µM)	P-CHO Rolling (IC_{50} µM)	L(pr) Rolling (IC_{50} µM)	L(er) Rolling (IC_{50} µM)
		$-CH_2-CH_3$	>5000	ni	533, 32	100		
		Na^+	1651, 4018, >5000, >5000	ni	514, 323	2500@4m		

Table F

The compound of Formula I wherein R^1, $R^{1'}$, $R^{3'}$, R^5, $R^{5'}$, R^6, and $R^{6'}$ are -H; R^2 is $-W'((CH_2)_m-(CHR^9)_q-(CH_2)_m-A')_t$; $R^{2'}$ is $-W((CH_2)_m-(CHR^9)_q-(CH_2)_m-A)_t$; R^3 is -OH; R^4 and $R^{4'}$ are $-COOR^{11}$; -W' is a covalent bond; W is -O-; m is 1; q is 1; R^9 is $-CH_3$; t is 1; and R^{11}, -A, and -A' are as in the table.

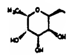
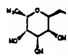
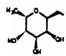
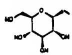
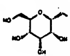
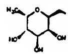
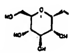
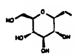
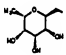
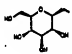
-A	-A'	R^{11}	E-COS (IC_{50} µM)	E-CHO Rolling (IC_{50} µM)	P-CHO (IC_{50} µM)	P-CHO Rolling (IC_{50} µM)	L(cv) Rolling (IC_{50} µM)	L(re) Rolling (IC_{50} µM)
		$-CH_2-CH_3$	895, 4906 807	nt	158, 1277 382, 74	100		
								
		$-CH_2-CH_3$	nt	nt	56, 399 1546, 1614	nt		
		Na^+	nt	nt		nt		
		$-CH_2-CH_3$		nt	247, 203	nt		

Table G

The compound of Formula I wherein R^1, $R^{1'}$, R^5, $R^{5'}$, R^6, and $R^{6'}$ are -H; R^2 is $-W((CH_2)_m-(CHR^9)_q-(CH_2)_m-A')_t$; $R^{2'}$ is $-W((CH_2)_m-(CHR^9)_q-(CH_2)_m-A)_t$; R^3 and $R^{3'}$ are -OH; R^4 and $R^{4'}$ are $-COOR^{11}$; -W is a covalent bond; m is 1; q is 1; R^9 is $-CH_3$; t is 1; and R^{11}, -A, and -A' are as in the table.

-A	-A'	R^{11}	E-COS (IC_{50} μM)	E-CHO Rolling (IC_{50} μM)	P-CHO (IC_{50} μM)	P-CHO Rolling (IC_{50} μM)	L(cv) Rolling (IC_{50} μM)	L(rc) Rolling (IC_{50} μM)
		$-CH_2-CH_3$	3232, >5000, >5000, >5000	100	1176, 359	10	10	
		-H	1623, >5000, >5000		901, 412	>2500		

Example C - Selectin Binding

An ELISA assay was employed that uses recombinant fusion proteins composed of extracellular portions of the human selectins joined to human immunoglobulin heavy chain CH_3, CH_2, and hinge regions. See, for example, Walz *et al.*, Science (1990) 250:1132; Aruffo et al., Cell (1991) 67:35; Aruffo *et al.*, Proc. Natl. Acad. Sci. USA (1992) 89:2292. The assay is well known in the art, and generally consists of the following three steps:

I. 2,3 sLe^x glycolipid (25 picomole/well) was transferred into microliter well as solutions and then evaporated off. Excess, which remained unattached, was washed off with water. The wells were then blocked with 5% BSA at room temperature for an hour and then washed with PBS containing 1mM calcium.

II. Preparation of "multivalent" receptor of the Selectin-IgG chimera was carried out by combining the respective chimera 1 µg/ml) with biotin labeled goat F(ab')2 anti-human IgG (Fc specific) and streptavidin-alkaline phosphatase diluted 1:1000 in 1% BSPBS (1 mM calcium) and incubating at 37 °C for 15 min. This allowed the soluble multivalent receptor complex to form.

III. Potential inhibitors such as compounds of formula I were allowed to react with the soluble receptor at 37°C for 45 min. This test assumes that optimal binding, between the soluble phase receptor complex and the inhibitor (non-natural

ligand), would have occurred within this time frame. This solution was then placed in the microliter wells that were prepared in step I. The plate was incubated at 37 C for 45 minutes to allow the soluble receptor to bind to its natural ligand. In the presence of a strong inhibitor only a few receptors should be free to bind to the microliter plate coated with the natural ligand.

The positive control is the signal produced by the soluble receptor when it is allowed to react with 2,3 sLe^X glycolipid in the microliter wells in the absence of any inhibitor. This was considered 100% binding. The signal produced by the receptor that had been previously treated with an inhibitor (recorded as O.D.), was divided by the signal produced by the positive control and multiplied by 100 to calculate the % receptor bound to the well, or the percent of control binding. Several of the compounds described herein were tested using this assay. Table H lists the extent to which some of the invention compounds inhibit binding of E, L and P-selectin to 2,3 sLe^X glycolipid in terms of IC_{50} values.

Table H

	HLSA E (μM)	HLSA L (μM)	HLSA P (μM)	P-CHO	B-CHO
	=>1000 =>1000 =>1000 =>1000 =>1000 =>1000	3112 319 366 >1000 706>1000 86>1000	39 141 1375>1000 395 386>1000 188>1000	40 316/1284/45 30/33 437/272 396/724/1784/358 34/1167/274/42	905
	=>1000	550	486 =>1000	1032, 468	
	=>1000	=>1000	=>1000	1053, 1998	
	=>1000	=>1000	=>1000	1741, 1902	
	=>1000	=>1000		1324, 2235 2848	

Table H (continued)

	ELISA				
	E (μM)	L (μM)	P (μM)	P-CHO	E-CHO
	=>1000	=>1000	=>1000	1923, 2626	
	=>1000	=>1000	=>1000	344, 836	
	=>1000	=>1000	=>1000	495, 1252	
	=>1000	=>1000	=>1000	862, 1044	
	=>1000	=>1000	=>1000		

Table H (continued)

	ELISA				
	E (uM)	L (uM)	P (uM)	P- CHO	E-CHO
	<=1000	<=1000	<=1000	226, 760, 1266	
	<=1000	<=1000	<=1000		
	<=1000	<=1000	<=1000		
	<=1000	<=1000	<=1000		

Table H (continued)

	BHSA				
	E (μM)	L (μM)	P (μM)	P-CHO	E-CHO
	=>1000	=>1000	=>1000		
	=>1000	=>1000	=>1000		
	=>1000	=>1000	=>1000	1595044428	
	=>1000	24	85	21	
	=>1000	14	37		

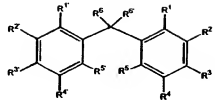
Table H (continued)

	ELISA				
	B (μM)	L (μM)	P (μM)	P-CHO	E-CHO
	331	184	224		
	112	30	42		

Based on the above results, it is apparent that the compounds of the invention are useful for treating diseases, preferably diseases that have an inflammatory component, such as Adult Respiratory Distress Syndrome (ARDS), ischemia and reperfusion injury, including strokes, mesenteric and peripheral vascular disease, organ transplantation, and circulatory shock (in this case one or many organs might be damaged following restoration of blood flow). Additionaly, by acting as antagonist ligand molecules, i.e. biochemical blocking agents that bind to selectins and prevent circulating leukocytes from binding to endothelial cells, the compounds of the invention are helpful in treating selectin-mediated conditions. These conditions include cancer, and particularly metastatic cancers, rheumatoid arthritis, asthma, dermatitis, inflammatory bowel disease, pulmonary inflammation, lung vasculitis, auto-immune conditions such as diabetes, and tissue rejection and other conditions such as obesity, cardiac injury, and thrombosis.

Claims

1. A compound of formula I:



wherein:

R^1, $R^{1'}$, R^2, $R^{2'}$, R^3, $R^{3'}$, R^4, $R^{4'}$, R^5, $R^{5'}$, R^6, and $R^{6'}$ are independently selected from the group consisting of:

A, B, Y-B, Y-C, -H, -OH, lower alkoxy, lower aryloxy, lower aralkoxy, lower alkoxyaryl, amino, alkyl of 1 to 4 carbon atoms optionally substituted with 1 to 2 lower alkyl groups,

$-W((CH_2)_n-A)_t$, $-W((CH_2)_m-(CHR^9)_q-(CH_2)_m-A)_t$,

$-O-CH_2-C\equiv C-A$, $-N(Ac)-CH_2-C\equiv C-A$, $-NH-CH_2-C\equiv C-A$,

$-N(CH_2-C\equiv C-A)_2$, $-N(Ac)CH_2Ar-A$, $-NHCH_2Ar-A$, $-N(CH_2Ar-A)_2$,

$-OCH_2Ar-A$, $-(C=O)(CH_2)_m-A$;

R^2 and R^3 or $R^{2'}$ and $R^{3'}$ may be taken together with the carbon atoms to which they are covalently bound to form a five or six membered ring optionally containing a heteroatom selected from the group consisting of -O-, -S-, and $-NR^{16}-$ wherein said five or six membered ring may further be substituted with one or more substituents selected from the group consisting of R^{16};

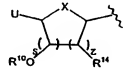
R^5 and $R^{5'}$ may optionally be taken together as $-CH_2-$, $-(C=O)-$, $-(CR^{16}_2)-$, $-O-$, $-S-$, and $-NR^{16}-$;

R^6 and $R^{6'}$ may optionally be taken together with the carbon atom to which they are covalently bound to form a $-(C=O)-$, $-(C=CH_2)-$, $-(C=C(R^{16})_2)-$, or $-(C=NR^{16})-$ group;

wherein:

A is selected from the group consisting of $-(C=O)R^{11}$, sialic acid, Kemp's acid, quinic acid, -B, $-SO_3M$, $-OSO_3M$, $-SO_2NH_2$, $-PO_3M'_2$, $-OPO_3M'_2$, $-NO_2$, saturated or unsaturated carboxylic acids of 1 to 4 carbon atoms, optionally substituted with 1 to 2 hydroxyl groups, and esters and amides of the carboxylic acid substituent;

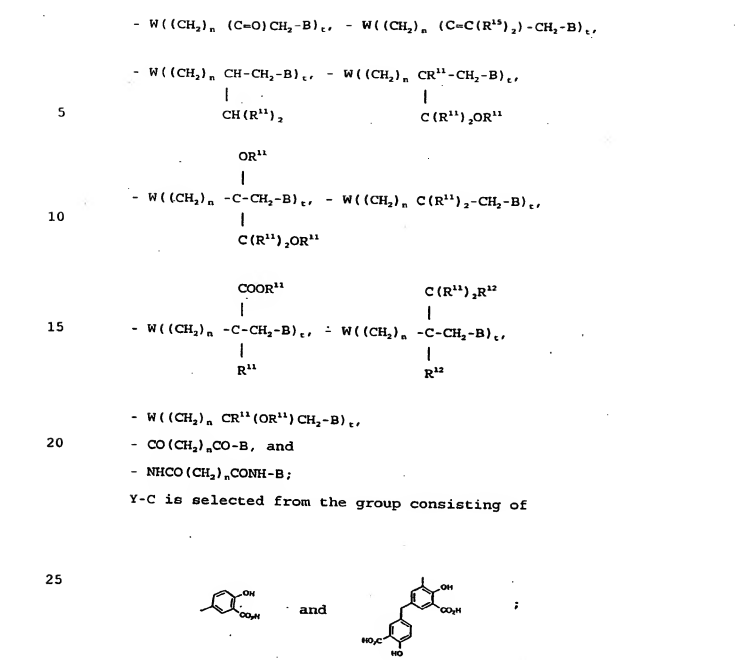
B is



wherein:

U is selected from the group consisting of $-R^9$, $-R^{10}$, $-CH_2OR^{10}$, $-CH_2O$-protecting group, $-COOR^{11}$, $-CON(R^{11})_2$, and $-COOM$;

Y-B is selected from the group consisting of



- $W((CH_2)_n\ (C{=}O)CH_2\text{-}B)_t$, - $W((CH_2)_n\ (C{=}C(R^{15})_2)\text{-}CH_2\text{-}B)_t$,

- $W((CH_2)_n\ CH(CH(R^{11})_2)\text{-}CH_2\text{-}B)_t$, - $W((CH_2)_n\ CR^{11}(C(R^{11})_2OR^{11})\text{-}CH_2\text{-}B)_t$,

- $W((CH_2)_n\ C(OR^{11})(C(R^{11})_2OR^{11})\text{-}CH_2\text{-}B)_t$, - $W((CH_2)_n\ C(R^{11})_2\text{-}CH_2\text{-}B)_t$,

- $W((CH_2)_n\ C(COOR^{11})(R^{11})\text{-}CH_2\text{-}B)_t$, - $W((CH_2)_n\ C(C(R^{11})_2R^{12})(R^{12})\text{-}CH_2\text{-}B)_t$,

- $W((CH_2)_n\ CR^{11}(OR^{11})CH_2\text{-}B)_t$,

- $CO(CH_2)_nCO\text{-}B$, and

- $NHCO(CH_2)_nCONH\text{-}B$;

Y-C is selected from the group consisting of

and ;

W is selected from the group consisting of a covalent bond, $-CH_2-$, $-(C{=}O)-$, $-(C{=}O)NH-$, $-O-$, $-N-$, $-S-$, $-NH-$, and $-NAc-$;

R^9 is lower alkyl of 1 to 4 carbon atoms;

each n is independently selected from the group 0, 1, 2, and 3;

each m is independently selected from the group 0, 1, 2, 3, and 4;

each q is independently selected from the group 0, 1, and 2;

each s is independently selected from the group 1, 2, and 3;

each z is independently selected from the group 1 and 2;

each t is independently selected from the group 1 and 2, with the proviso that when W is $-N<$, then t is 2, and for all other definitions of W, t is 1;

R^{10} is selected from the group consisting of -H, $-R^{11}$, $-SO_3M$, $-(C=O)R^{11}$, $-SO_2NH_2$, $-PO_3M_2$, -alk-$COOR^{13}$, alk-$CON(R^{11})_2$, and -O-carbohydrate;

R^{11} is independently selected from the group consisting of -H, lower alkyl of 1 to 4 carbon atoms, cyclic alkyl of 5 to 6 carbon atoms, heterocyclic alkyl of 4 to 5 carbon atoms and 1 to 2 heteroatoms, aryl and aralkyl;

R^{12} is selected from the group consisting of $-N(R^{11})_2$ and $-SR^{11}$;

R^{13} is selected from the group consisting of R^{11} and M;

R^{14} is selected from the group consisting of -H and $-OR^{10}$, with the proviso that when z is 2, then together the two R^{14} groups may form a double bond;

R^{15} is independently selected from the group consisting of $-R^{11}$ and -COOH;

R^{16} is independently selected from the group consisting of $-R^{9}$, $-R^{10}$, $-CH_2OR^{10}$, $-CH_2O$-protecting group, $-COOR^{11}$, $-CON(R^{11})_2$, and -COOM;

M is selected from the group consisting of Na^+, K^+, Mg^{2+}, and Ca^{2+};

M' is selected from the group consisting of -H, -M, and R^9;

X is selected from the group consisting of -O-, -S-, $-C(R^{11})_2-$, and $-N(R^{11})-$; and pharmaceutically acceptable salts thereof with the provisos that:

at least one of R^1, R^2, R^3, R^4, R^5, $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{5'}$, R^6, and $R^{6'}$ is selected from the group consisting of saturated or unsaturated carboxylic acids of 1 to 4 carbon atoms, optionally substituted with 1 to 2 hydroxyl groups, and esters and amides of the carboxylic acid substituent; and

at least one of R^1, R^2, R^3, R^4, R^5, $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{5'}$, R^6, and $R^{6'}$ is a substituent containing a B group.

2. The compounds of claim 1 wherein at least one of R1, R2, R3, R4, R5, R1', R2', R3', R4', R5', R6, and R6' are independently selected from the group consisting of

$-W(CH_2(C=O)CH_2-B)_t$, $-W(CH_2(C=C(R^{15})_2)-CH_2-B)_t$,

$-W(CH_2CH(CH(R^{11})_2)-CH_2-B)_t$, $-W((CH_2)_n-B)_t$,

$-W(CH_2-C(OR^{11})(C(R^{11})_2OR^{11})-CH_2-B)_t$, $-W(CH_2C(R^{11})_2-CH_2-B)_t$, and

$-W(CH_2-CR^{11}(OR^{11})CH_2-B)_t$

wherein W is a covalent bond or -O-, and t is 1.

3. The compounds of claim 1 wherein R^4 and $R^{4'}$ are $-COOR^{11}$.

4. The compounds of claim 3 wherein $R^{3'}$ is -OH.

5. The compounds of claim 4 wherein R^3 is

$-W((CH_2)_m-(CHR^9)_q-(CH_2)_m-A)_t$, and -W is -O-.

6. The compounds of claim 4 wherein $R^{2'}$ is

$-W((CH_2)_m-(CHR^9)_q-(CH_2)_m-A)_t$; R^3 is $-W((CH_2)_m-(CHR^9)_q-(CH_2)_m-A)_t$; the $R^{2'}$ -W is a covalent bond and the $R^{3'}$ W is -O-.

7. The compounds of claim 3 wherein R^3 and $R^{3'}$ are -OH.

8. The compounds of claim 7 wherein R^2 is $-W((CH_2)_m-(CHR^9)_q-(CH_2)_m-A)_t$, and -W is a covalent bond.

9. The compounds of claim 7 wherein R^2 and $R^{2'}$ are $-W((CH_2)_m-(CHR^9)_q-(CH_2)_m-A)_t$, and -W is a covalent bond.

10. The compounds of claim 3 wherein R^3 and $R^{3'}$ are $-W((CH_2)_m-(CHR^9)_q-(CH_2)_m-A)_t$, and -W is -O-.

11. The compounds of claims 3-9 or 10 wherein m is 1; q is 1; R^9 is $-CH_3$; and t is 1.

12. The compounds of claim 11 wherein A is B.

13. The compounds of claim 1 wherein B is selected from the group consisting of glucose, fucose, galactose, mannose, and arabinose.

14. The compounds of claim 1 wherein M is Na^+.

15. The compounds of claim 1 wherein M' is selected from the group consisting of -H, Na+, and -CH3.

16. The compounds of claim 1 wherein X is -O-.

17. The compounds of claim 1 wherein U is selected from the group consisting of $-CH_2OR^{10}$ and $-R^9$.

18. The compounds of claim 1 wherein W is selected from the group consisting of a covalent bond and -O-, and t is 1.

19. The compound of claim 1 wherein R^4 and $R^{4'}$ are independently selected from saturated or unsaturated carboxylic acids of 1 to 4 carbon atoms, optionally substituted with 1 to 2 hydroxy groups, and esters and amides thereof, and at least one of R^2, $R^{2'}$, R^3, $R^{3'}$, R^6, and $R^{6'}$ is selected from the group consisting of

$-W((CH_2)_n-B)_t$,

$-W(CH_2(C=O)CH_2-B)_t$, $-W(CH_2(C=C(R^{15})_2)-CH_2-B)_t$,

$-W(CH_2-\underset{\displaystyle C(R^{11})_2OR^{11}}{\overset{\displaystyle OR^{11}}{C}}-CH_2-B)_t$, and $-W(\underset{\displaystyle CH(R^{11})_2}{CH}-CH_2-B)_t$,

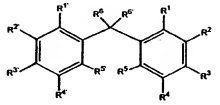
where W is a covalent bond or -O- and t is 1, and wherein s is 1 or 2, R^{14} is -H or -OH, X is -O-, U is $-CH_2OR^{10}$ or $-R^9$, and R^{10} is -alk-COOH, $-SO_3M$, -H, or -alk-COOM.

20. The compound of claim 1 wherein R^2 is Y-C.

21. A pharmaceutical composition comprising at least one compound of claim 1 and a pharmaceutically acceptable carrier.

22. A method of treating selectin-mediated disorders comprising the step of:

administering to a patient in need thereof a therapeutically effective amount of a compound of formula I:



wherein:

R^1, $R^{1'}$, R^2, $R^{2'}$, R^3, $R^{3'}$, R^4, $R^{4'}$, R^5, $R^{5'}$, R^6, and $R^{6'}$ are independently selected from the group consisting of:

A, B, Y-B, Y-C, -H, -OH, lower alkoxy, lower aryloxy, lower aralkoxy, lower alkoxyaryl, amino, alkyl of 1 to 4 carbon atoms optionally substituted with 1 to 2 lower alkyl groups,

$-W((CH_2)_n-A)_t$, $-W((CH_2)_m-(CHR^9)_q-(CH_2)_m-A)_t$,

$-O-CH_2-C\equiv C-A$, $-N(Ac)-CH_2-C\equiv C-A$, $-NH-CH_2-C\equiv C-A$,

$-N(CH_2-C\equiv C-A)_2$, $-N(Ac)CH_2Ar-A$, $-NHCH_2Ar-A$, $-N(CH_2Ar-A)_2$

$-OCH_2Ar-A$, $-(C=O)(CH_2)_m-A$;

R^2 and R^3 or $R^{2'}$ and $R^{3'}$ may be taken together with the carbon atoms to which they are covalently bound to form a five or six membered ring optionally containing a heteroatom selected from the group consisting of -O-, -S-, and $-NR^{16}-$ wherein said five or six membered ring may further be substituted with one or more substituents selected from the group consisting of R^{16};

R^5 and $R^{5'}$ may optionally be taken together as

$-CH_2-$, $-(C=O)-$, $-(CR^{16}_2)-$, $-O-$, $-S-$, and $-NR^{16}-$;

R^6 and $R^{6'}$ may optionally be taken together with the carbon atom to which they are covalently bound to form a $-(C=O)-$, $-(C=CH_2)-$,

$-(C=C(R^{16})_2)-$, or $-(C=NR^{16})-$ group;

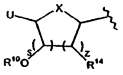
wherein:

A is selected from the group consisting of

$-(C=O)R^{11}$, sialic acid, Kemp's acid, quinic acid,

-B, $-SO_3M$, $-OSO_3M$, $-SO_2NH_2$, $-PO_3M'_2$, $-OPO_3M'_2$, $-NO_2$, saturated or unsaturated carboxylic acids of 1 to 4 carbon atoms, optionally substituted with 1 to 2 hydroxyl groups, and esters and amides of the carboxylic acid substituent;

B is



wherein:

U is selected from the group consisting of $-R^9$, $-R^{10}$, $-CH_2OR^{10}$, $-CH_2O$-protecting group, $-COOR^{11}$, $-CON(R^{11})_2$, and -COOM;

Y-B is selected from the group consisting of

- $W((CH_2)_n(C{=}O)CH_2\text{-}B)_t$, - $W((CH_2)_n(C{=}C(R^{15})_2)\text{-}CH_2\text{-}B)_t$,

- $W((CH_2)_n CH(CH(R^{11})_2)\text{-}CH_2\text{-}B)_t$, - $W((CH_2)_n CR^{11}(OR^{11})\text{-}CH_2\text{-}B)_t$,

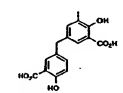
- $W((CH_2)_n C(C(R^{11})_2OR^{11})(COOR^{11})\text{-}CH_2\text{-}B)_t$, - $W((CH_2)_n C(C(R^{11})_2R^{12})(R^{11})\text{-}CH_2\text{-}B)_t$,

- $W((CH_2)_n CR^{11}(OR^{11})CH_2\text{-}B)_t$,

- $CO(CH_2)_nCO\text{-}B$, and

- $NHCO(CH_2)_nCONH\text{-}B$;

Y-C is selected from the group consisting of


and

;

W is selected from the group consisting of a covalent bond, $-CH_2-$, -(C=O)-, -(C=O)NH-, -O-, -NR^9-, -S-, -NH-, and -NAc-;

R^9 is lower alkyl of 1 to 4 carbon atoms;

each n is independently selected from the group 0, 1, 2, and 3;

each m is independently seleeted from the group 0, 1, 2, 3, and 4;

each q is independently selected from the group 0, 1, and 2;

each s is independently selected from the group 1, 2, and 3;

each z is independently selected from the group 1 and 2;

each t is independently selected from the group 1 and 2, with the proviso that when W is  , then t is 2, and for all other definitions of W, t is 1;

R^{10} is selected from the group consisting of -H, $-R^{11}$, $-SO_3M$, $-(C=O)R^{11}$, $-SO_2NH_2$, $-PO_3M_2$, -alk-$COOR^{13}$, alk-$CON(R^{11})_2$, and -O-carbohydrate;

R^{11} is independently selected from the group consisting of -H, lower alkyl of 1 to 4 carbon atoms, cyclic alkyl of 5 to 6 carbon atoms, heterocyclic alkyl of 4 to 5 carbon atoms and 1 to 2 heteroatoms, aryl and aralkyl;

R^{12} is selected from the group consisting of $-N(R^{11})_2$ and $-SR^{11}$;

R^{13} is selected from the group consisting of R^{11} and M;

R^{14} is selected from the group consisting of -H and $-OR^{10}$, with the proviso that when z is 2, then together the two R^{14} groups may form a double bond;

R^{15} is independently selected from the group consisting of $-R^{11}$ and -COOH;

R^{16} is independently selected from the group consisting of $-R^9$, $-R^{10}$, $-CH_2OR^{10}$, $-CH_2O$-protecting group, $-COOR^{11}$, $-CON(R^{11})_2$, and $-COOM$;

M is selected from the group consisting of Na^+, K^+, Mg^{2+}, and Ca^{2+};

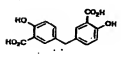
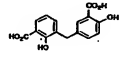
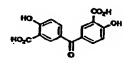
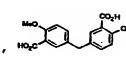
M' is selected from the group consisting of -H, -M, and R^9;

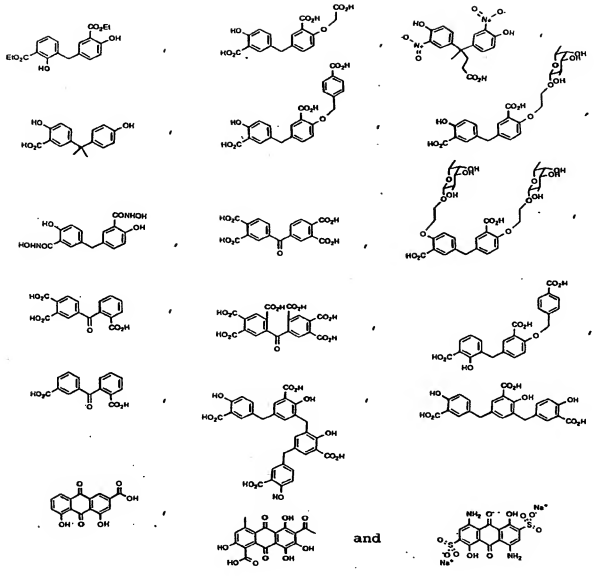
X is selected from the group consisting of -O-, -S-, $-C(R^{11})_2-$, and $-N(R^{11})-$; and pharmaceutically acceptable salts thereof with the proviso that at least three of R^1, R^2, R^3, R^4, R^5, $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{5'}$, R^6, and $R^{6'}$ are not -H.

23. The method of claim 22 wherein at least one of R^1, R^2, R^3, R^4, R^5, $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{5'}$, R^6, and $R^{6'}$ is a substituent containing a B group.

24. The method of claim 22 wherein the selectin-mediated disorder is selected from the group consisting of cancer, autoimmune disorders and inflammation.

25. The method of claim 22 wherein the compound is selected from the group consisting of


and